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Heptachlor in Relation to Man and the Environment

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HEPTACHLOR IN RELATION TO MAN AND THE ENVIRONMENT

Prepared July 1972
Amended March 1975

Criteria and Evaluation Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
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PREFACE

Because of the Environmental Protection Agency's statutory mandate to protect the public health and well being of its citizenry through control of economic poisons, a comprehensive effort intended to insure intensive and regular review of all economic poisons was initiated March 18, 1971, to identify those pesticides which could represent potential unreasonable adverse effects on man and his environment. Since that date comprehensive "internal reviews" have been conducted by staff of the Office of Pesticide Programs on a number of pesticides. The initial direction for this program came in a statement outlined by the Administrator of the Environmental Protection Agency on March 18, 1971.

This report on heptachlor was conducted from 1971 to 1972. The chemistry and methodology section was amended in 1975. Other sections were updated in a separate report entitled: Pesticidal Aspects of Chlordane and Heptachlor in Relation to Man and the Environment - A Further Review, 1972-1975.

This review evaluates scientific data in the areas of fish, wildlife, distribution in the environment (air, soil, water), residues in crops and food items, and toxicology and epidemiology.

This review summarizes rather than interprets scientific data studied during the process of reviewing chlordane. It is not intended that this report correlate data from different sources. The review also does not present opinions on contradictory findings.

The review of heptachlor covers all uses of the pesticide in the United States and should be applicable to future needs in the Agency. The review was researched and prepared by the Special Pesticides Review Group, Office of Pesticide Programs, Environmental Protection Agency.

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HEPTACHLOR--A REVIEW OF ITS USES, CHEMISTRY, ENVIRONMENTAL HAZARDS, AND TOXICOLOGY

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SUMMARY

Heptachlor is a chlorinated hydrocarbon pesticide and is a member of the group of cyclodiene insecticides which includes aldrin, dieldrin, heptachlor, endrin, thiodan, chlordane, and telodrin. Technical heptachlor is not a single entity but rather a mixture of heptachlor and related synthetic products. Technical heptachlor is manufactured by a controlled process which yields a product with a relatively consistent composition. This consistency is said to have permitted the chemical evaluation of its formulations and residues.

Heptachlor has been registered in the United States as an insecticide for use in agriculture, home lawns, gardens, and structural pest control since 1952. The early registered uses of heptachlor included foliar and soil application for termite control and 70% for control of agricultural soil pests. Of the total used in the United States in 1971 over 98% was used for soil application in agriculture and termite control. The present soil uses of heptachlor account for over 98% of annual production. Twenty-eight percent is used for termite control and 70% for control of agricultural soil pests.

As with chlordane, heptachlor is used primarily as a soil insecticide. Therefore, any consideration of possible environmental effects must place emphasis on the fate of heptachlor in the soil. In most of the registered uses, the rates, methods of application, and the environmental conditions vary. However, while these factors may differ, the controlling factors are the characteristics of heptachlor. These are persistence and relative immobility in the soil. Certain organisms in the environment do bioconcentrate heptachlor, but it apparently does not build up in the food chain.

Heptachlor has been reported to be less persistent in the soil than chlordane, although it may be detected in the soil for as long as ten years after application. Heptachlor may vaporize slowly from the soil; it may be oxidized to form heptachlor epoxide, a substance more persistent and toxic than the parent compound; or it may be converted to less toxic metabolites by soil bacteria. Heptachlor is relatively immobile in the soil, and various workers have demonstrated that the majority of the residues are in the top few inches of the soil.

Several studies indicate that contamination of water by heptachlor is not a widespread problem. However, residues of heptachlor have been found in fish from various bodies of water. In general, the values found have been less than 5. Fish examined from the Pacific Ocean have shown detectable levels and oysters taken from the South Atlantic and Gulf of Mexico have demonstrated levels of heptachlor up to 10 ppb.

Tolerances for heptachlor have been established by the U.S. Environmental Protection Agency at 0.1 ppm for cabbages, snap beans, lettuce and rutabagas. Zero or interim tolerances are in effect for barley, beans, blackberries, blueberries, boysenberries, chestnuts, citrus, corn, cotton, cranberries, dewberries, oats, peaches, pears, peppers, pineapples, raspberries, rice, rye, sorghum, soybeans, tomatoes and wheat.

In 1969 the Secretary's Commission on Pesticides and Their Relationship to the Environmental Health recommended restricting the use of certain persistent pesticides in the United States to specific essential uses which create no hazard to the quality of the environment or to human health. Heptachlor was included in this recommendation.

In a statement issued on March 18, 1971, the Administrator of the Environmental Protection Agency reported: "Active internal review is being initiated as to the registration of products containing benzene hexachloride, lindane, chlordane, endrin, heptachlor and toxaphene, all products containing mercury, arsenic, or lead and all others deemed necessary to review. . . ." In accordance with this charge, the Special Pesticides Review Group has reviewed the hazards associated with the use of heptachlor.

CHAPTER I

Current Heptachlor Pesticide Uses, Their Impact on the Environment and Alternatives

The patterns of use for heptachlor have changed since it was first registered in 1952. Prior to 1960, the registered uses included house and garden applications, termite control and soil and foliar applications on sugar beets, vegetables, forage crops, cereal, oil and seed crops. The use of heptachlor as a foliar agricultural insecticide is now very limited.

The persistent qualities of heptachlor and heptachlor-epoxide became apparent with the development of more sensitive analytical methods. The residues of heptachlor in soil and translocation and absorption by plants were recognized as means of food chain contamination. Certain uses of heptachlor were eliminated in order to prevent the contamination of milk, meat, and other food products. Heptachlor is manufactured by Velsicol Chemical Company, and 312 products are registered by 112 formulators throughout the United States. Heptachlor formulated as an emulsible concentrate may contain 2 and 3 lb active toxicant; granules may contain 2.5, 5, 10, 20, and 25% active toxicant; oil solutions may contain 2, 3 and 3.3 lb/gal; dust concentrates and wettable powders usually contain 25% active components.

Heptachlor is used primarily for control of soil pests. Other agricultural uses include: seed treatment; transplanting water treatments; certain treatments for fire ant control; foliar applications to pineapple and certain limited usage on ditchbanks, field borders, roadsides, vacant fields in forestry and as a household insecticide. Nonagricultural uses include treatments of lawns, nursery soil and ornamental turf. It is also used as a mosquito larvicide and as a termite soil poison.

Over 98 percent of the heptachlor sold in 1971 was used as a soil treatment. Seventy percent was used as a soil insecticide to control agricultural pests. Twenty-eight percent was used to control termites. The registered uses for heptachlor, tolerances, dosages, limitation of application and possible substitutes for registered uses are presented in Table 1 of this chapter. The following general limitations are imposed with these uses:

1. Grazing is not allowed wherever heptachlor is applied.
2. Soil applications are limited to one treatment per year unless specified otherwise.
3. While the use of heptachlor may be essential under certain conditions (for example, public health, protection of food, feed, fiber, quarantine and forest pests), no general registration for such uses has been granted.

I. A.

Table 1. Summary of Registered Heptachlor Uses and Alternatives

Crop or Use	Tolerance (ppm)	Dosage (lb AI/acre)	Limitations	Pests	Alternatives
Foliar					
Pineapples	0 Extended	2.0	60 days	Ants	Chlordane
Ditch banks, Field borders, Roadsides, Vacant lands	NF	2-3 oz/acre		Grasshoppers	Carbaryl Chlordane Malathion Toxaphene Naled
Soil					
Barley	0 Extended	3.0	Preplanting soil application only.	Cutworms White grubs Wireworms	Chlordane Chlordane Chlordane
Beans (snap)	0.1	2.5	Preplanting soil application only. Work into soil.	Cutworms	Chlordane Diazinon Parathion Toxaphene
				White-fringed beetle larvae White grubs	Chlordane Chlordane Parathion
				Wireworms	Chlordane Diazinon Parathion

Table 1. (Continued)

Crop or Use	Tolerance (ppm)	Dosage (lb AI/acre)	Limitations	Pests	Alternatives
Lettuce	0.1	3.0	Preplanting soil application only. Work into soil.	Cutworms	Chlordane Diazinon Lindane Parathion Toxaphene
				Japanese beetle larvae	Chlordane Lindane Parathion
				Root maggots	Chlordane Diazinon Lindane
				White grubs	Chlordane Lindane Parathion
				Wireworms	Chlordane Diazinon EDB, Lindane Parathion
Oats	0 Extended	3.0	Preplanting soil application only.	Cutworms White grubs Wireworms	Chlordane
Rice	Extended	3.0	Preplanting soil application only.	Rice water weevils	
Rutabagas	0.1	5.0	Preplanting soil application to furrow or broadcast. Work into soil.	Cutworms Japanese beetles White grubs Wireworms	Chlordane Parathion

Table 1. (Continued)

Crop or Use	Tolerance (ppm)	Dosage (lb AI/acre)	Limitations	Pests	Alternatives
Rye	0	3.0	Preplanting soil application only.	Cutworms White grubs Wireworms	Chlordane
Pineapples	0	3.0	Preplanting soil application only.		
Soybeans	Extended	3.0	Preplanting soil application (or at time of planting). Do not contaminate food or feedstuffs.	Cutworms Grape colaspis	Chlordane Diazinon
				Japanese beetle larvae	Chlordane
				Seed-corn maggots	Chlordane
				White-fringed beetles	Chlordane
				White grubs	Parathion
				Wireworms Cutworms	Chlordane Chlordane
Cabbage	0.1	0.25	Soil application to furrow at time of planting or transplanting.	Cabbage maggot Cutworms	Chlordane Chlordane
Wheat	0 Extended	3.0	Preplanting soil application only.	Cutworms White grubs Wireworms	Chlordane

Table 1. (Continued)

Crop or Use	Tolerance (ppm)	Dosage (lb AI/acre)	Limitations	Pests	Alternatives
Blackberries Boysenberries Dewberries Raspberries	Extended	4.0	Soil application only. Do not apply after edible parts start to form.	Cutworms Japanese beetle larvae Strawberry root weevil larvae White-fringed beetle larvae White grubs Wireworms	Chlordane Chlordane Chlordane Chlordane Chlordane
Blueberries	Extended	4.0	Soil application only. Do not apply after edible parts start to form.	Cutworms Japanese beetle larvae Strawberry root weevil larvae White-fringed beetle larvae White grubs Wireworms Root weevils	Chlordane
Citrus	Extended	3.0	Soil application only. Apply under trees without pressure.	Argentine ant Citrus root weevils Fuller's rose beetles	Chlordane Chlordane
Corn	0 Extended	3.0	Soil application only.	Corn billbugs Cornfield ant	Chlordane
		5.0	Soil application to peat or muck soils only.	Corn rootworms	Buxten, Carbofuran, Chlordane, Dasanit, Disyston, Phorate, Dyfonate

Table 1. (Continued)

Crop or Use	Tolerance (ppm)	Dosage (lb AI/acre)	Limitations	Pests	Alternatives
Corn		3.0	Preplanting or at time of planting.	Cutworms	Carbofuran Diazinon Parathion
				Grape colaspis Green June beetle larvae	Chlordane
				Japanese beetle larvae	Chlordane Parathion
				Rough-headed cornstalk beetles (Sugarcane beetle).	
				Seed-corn beetles	Chlordane Thimet(R)*
				Seed-corn maggots	Chlordane
				White-fringed beetle larvae	Chlordane
				White grubs	Chlordane Parathion
				Wireworms	Chlordane Diazinon Parathion
				Asiatic garden beetle larvae	
				Flea beetle larvae	Chlordane

* Phorate

Table 1. (Continued)

Crop or Use	Tolerance (ppm)	Dosage (lb AI/acre)	Limitations	Pests	Alternatives
				False wireworms	Chlordane
				Maize billbugs	Chlordane
				Masked chafer larvae	Chlordane
				Sod webworms	Chlordane
Peaches	0 Extended	3.0	Ground cover application in spring before petal fall.	Consperse stink bugs	
				Plum curculios	Chlordane
Pears	Extended	3.0	Ground cover application in spring before petal fall.	Consperse stink bugs	
Peppers	Extended	3.0	Soil application only. Do not apply after edible parts start to form.	Cutworms	Chlordane Diazinon Lindane Parathion Toxaphene
				Japanese beetle larvae	Chlordane Lindane Parathion
				Root maggots	Chlordane Diazinon Lindane

Table 1. (Continued)

Crop or Use	Tolerance (ppm)	Dosage (lb AI/acre)	Limitations	Pests	Alternatives
				White grubs	Chlordane Lindane Parathion
				Wireworms	Chlordane Lindane Parathion
Rutabagas		3.0	Soil application soon after plants emerge with a second applica-tic 3-4 weeks later. Do not use tops as food or feed.	Japanese beetle larvae	Chlordane Parathion
				Root maggots	Chlordane
				White-fringed beetle larvae	Chlordane
				White grubs	Chlordane Parathion
				Wireworms	Chlordane Parathion
Tobacco		3.0	Apply broadcast to soil and work into top few inches.	White-fringed beetle larvae	Chlordane
				White grubs	Chlordane
			Apply broadcast.	Wireworms	Chlordane Diazinon Dyfonate Parathion
			Apply as transplant solution.	Wireworms	

Table 1. (Continued)

Crop or Use	Tolerance (ppm)	Dosage (lb AI/acre)	Limitations	Pests	Alternatives
Tomatoes	0 Extended	3.0	Soil application. Do not apply after edible parts start to form.	Cutworms	Toxaphene Chlordane Diazinon Lindane Parathion
				Japanese beetle larvae	Chlordane Lindane Parathion
				White-fringed beetle larvae	Chlordane
				White grubs	Chlordane Lindane Parathion
				Wireworms	Chlordane Diazinon EDB Lindane Parathion
Restricted Field Application	Nonfood	2.0	Soil application.	Imported fire ant	Mirex
Seed Treatment					
Barley		2.0 oz/bu seed	Seed treatment. Do not use as food or feed.	Corn rootworms Seed-corn beetles Wireworms	Chlordane Lindane

Table 1. (Continued)

Crop or Use	Tolerance (ppm)	Dosage (lb AI/acre)	Limitations	Pests	Alternatives
Beans	Extended	2.0 oz/bu seed	Seed treatment. Do not use as food or feed.	Corn rootworms Seed-corn beetles Wireworms	Chlordane Diazinon Lindane
Corn		2.0 oz/bu seed	Seed treatment. Do not use as food or feed.	Corn rootworms Seed-corn beetles Wireworms	Chlordane Diazinon Lindane
Cotton	Extended	2.0 oz/bu seed	Seed treatment. Do not use as food or feed.	Corn rootworms Seed-corn beetles Wireworms False wireworms	Chlordane Lindane
Oats		2.0 oz/bu seed	Seed treatment. Do not use as food or feed.	Corn rootworms Seed-corn beetles Wireworms	Chlordane Lindane
Rice		2.0 oz/bu seed	Seed treatment. Do not use as food or feed.	Corn rootworms Seed-corn beetles Wireworms Rice water beetles	Chlordane Lindane
Rye		2.0 oz/bu seed	Seed treatment. Do not use as food or feed.	Corn rootworms Seed-corn beetles Wireworms	Chlordane Lindane
Sorghum	Extended	2.0 oz/bu seed	Seed treatment. Do not use as food or feed.	Corn rootworms Kafir ants	Chlordane
				Seed-corn beetles Wireworms	Chlordane Lindane
				False wireworms	

Table 1. (Continued)

Crop or Use	Tolerance (ppm)	Dosage (lb AI/acre)	Limitations	Pests	Alternatives
Soybean		2.0 oz/bu seed	Seed treatment. Do not use as food or feed.	Corn rootworms Seed-corn beetles Wireworms	Chlordane Diazinon Lindane
Wheat		2.0 oz/bu seed	Seed treatment. Do not use as food or feed.	Corn rootworms Seed-corn beetles Wireworms	Chlordane Lindane
Transplant water and dust					
Cabbage		0.03% (in water)	Transplant water. Drench soil around plants.	Green June beetle larvae Japanese beetle larvae White grubs Wireworms	
		1.0 (dust)	Apply to soil around plants immediately after transplanting.		
		2.5 (dust)	Apply to roots and stems of plants prior to transplanting.		
Tobacco	NF	1 oz actual per 50 gal of water	Use as transplanting water when tobacco plants are set in field. Use a minimum of 200 gallons per acre.	White-fringed beetle larvae	Chlordane
				Wireworms	Chlordane Diazinon Lindane
Bait					
Soybeans		4 oz actual per 50 lb of bran/acre	Bait application. Apply broadcast before setting and near plants after setting.	Cutworms	Chlordane

Table 1. (Continued)

Crop or Use	Tolerance (ppm)	Dosage (lb AI/acre)	Limitations	Pests	Alternatives
Non agricultural uses					
Forestry plantation	NF	Apply 1% or 2% spray in water with sticker to upper half of tree leaves during March or early April.		White-pine weevils	
Subterranean termites in premises					
		0.5% to 1% in water using standard foundation trenching and treatment methods.			Chlordane
Lawns, nursery soil, ornamentals, turf (soil)					
	NF	2%		Ants	Carbaryl Diazinon Mirex bait
				Asiatic garden beetle larvae	Chlordane
				Boxelder bugs	Chlordane Diazinon
				Ticks	Carbaryl Chlordane Diazinon
				White-fringed beetle larvae	Chlordane
				White grubs	Chlordane
				Wireworms	Chlordane

Table 1. (Continued)

Crop or Use	Tolerance (ppm)	Dosage (lb AI/acre)	Limitations	Pests	Alternatives
Lawns, nursery soil, ornamentals, turf (soil)					
	NF	2%		Armyworms	Diazinon
				Cutworms	
				Lawn chinch bugs	Akton
				Sod webworms	
				Black vine weevils	Chlordane
				Chiggers	Chlordane Diazinon
				Earwigs	Carbaryl Chlordane Diazinon
				European chafer larvae	Chlordane
				Fleas	Carbaryl
				Grasshoppers	
				Green June beetles	Chlordane
				Japanese beetle larvae	Chlordane
				Mole crickets	Diazinon
				Mosquitoes (adult)	Carbaryl Chlordane

Table 1. (Continued)

Crop or Use	Tolerance (ppm)	Dosage (lb AI/acre)	Limitations	Pests	Alternatives
Lawns, nursery soil, ornamentals, turf (soil)					
	NF	2%		Pillbugs Snails Sowbugs Striped grassworms	
				False wireworms European crane flies Earthworms	
Flower garden plants, ornamentals and shade trees					
	NF	3.0 lb/100 gal. (foliar)		Black vine weevil adults	Chlordane Thiodan
			Soil	Black vine weevil larvae	Chlordane
			Soil surface	Imported fire ants	Chlordane Mirex bait
				Narcissus bulb flies	Chlordane Dylox
				White grubs	Chlordane
				Wireworms	Chlordane (soil)
			Foliar	Japanese beetle adults	Carbaryl Malathion

Table 1. (Continued)

Crop or Use	Tolerance (ppm)	Dosage (lb AI/acre)	Limitations	Pests	Alternatives
Flower garden plants, ornamentals and shade trees				Strawberry root weevils Brachyrhinus rugosotriatus Bulb flies Earwigs Root weevils	
	NF	3.0 lb/100 gal (foliar)			
Household and Commercial (Spot residual applications)					
	NF	0.5% in petroleum distillate or water.		Ants	Baygon, Chlordane, Diazinon, Lindane, Malathion, Pyrethrins, Ronnel, synergized Pyrethrins
				Boxelder bugs	Chlordane, Lindane Malathion
			Do not treat animals.	Brown dog ticks	Baygon, Chlordane, Diazinon, Lindane, Malathion, Ronnel
				Carpet beetles	Baygon, Chlordane, Diazinon, Lindane, Malathion, Ronnel
				Centipedes	Baygon, Chlordane, Lindane, Malathion
				Crickets	Baygon, Chlordane, Lindane
				House flies	Baygon, Chlordane, Lindane, Ronnel

Table 1. (Continued)

Crop or Use	Tolerance (ppm)	Dosage (lb AI/acre)	Limitations	Pests	Alternatives
Household and Commercial (Spot residual applications)				Mosquitoes	Baygon, Chlordane, Diazinon, Lindane, Malathion, Ronnel
	NF	0.5% in petroleum distillate or water.		Roaches	Baygon, Chlordane, Diazinon, Lindane, Malathion, Pyrethrins, Ronnel, synergized Pyrethrins
				Scorpions	Baygon, Chlordane Diazinon, Lindane, Malathion
				Spiders	Baygon, Chlordane, Diazinon, Lindane, Malathion, Ronnel
				Silverfish	Baygon, Chlordane, Diazinon, Lindane. Malathion, Ronnel
				Wasps	Baygon, Chlordane, Lindane, Malathion
				Waterbugs	Baygon, Chlordane, Diazinon, Lindane, Malathion, Pyrethrins, Ronnel, synergized Pyrethrins
				Firebrats Old-house borers Powder-post beetles	

Table 1. (Continued)

Crop or Use	Tolerance (ppm)	Dosage (lb AI/acre)	Limitations	Pests	Alternatives
Public Health	NF	0.8 oz to 1.6 oz actual in spray application (ground). 1.6 oz to 2.0 oz spray application (air). 5% granular - 0.8 oz to 1.6 oz per acre.		Mosquito larvae	Abate, EPN, Fenthion, Lindane, Malathion, Parathion, Paris green

I.B. Discussion of the Impact of Heptachlor Uses on the Environment and the Alternatives - The Special Pesticide Review Group has studied the hazards to man and the environment associated with the use of heptachlor as a pesticide in the United States. In making this study, the Group has consulted pesticide experts in EPA and other Federal Agencies and has evaluated the information received in response to the Federal Register notice on chlordane and heptachlor (37FR6606). The Group considered, but was not able to fully evaluate, the social and economic effects which would result from the cancellation of specific uses of heptachlor as a pesticide.

In an effort to evaluate the environmental and human health effects of heptachlor, broad use patterns were established by the Special Pesticide Review Group. Basically, the uses were grouped into four broad categories: (1) foliar; (2) soil treatment; (3) seed treatment; and, (4) special uses. The significant uses of heptachlor include application to agricultural crops, home gardens, ornamental plants, hawns, and to houses or other premises for termit control. These broad use patterns present distinctly different degrees of hazard to human health, wildlife and the environment.

The following is a review of the broad use patterns as established for the systematic consideration of the safety of this pesticide.

I.B.1. Foliar Applications - Foliar applications present the highest degree of hazard involved in the various methods of applying heptachlor, especially in terms of environmental contamination, direct human exposure and hazards resulting from chemical residues in food or feed crops. Dusts or sprays for foliar applications have the folowing adverse characteristics: (1) they are subject to drift thus contaminating food crops or water outside of the desired area of application; (2) much of the applied pesticide may not reach the target area; and, (3) deposits of pesticide may be left on the foliage of the crops and may contaminate the edible portions either by direct applicaton or by drift.

I.B.1.a. Agricultural Crops - All foliar applications of heptachlor on agricultural crops, except ant control on pineapples in Hawaii, have alternate pesticides. However, some of the alternates present a greater acute toxicity hazard to man and the environment than heptachlor when used as a foliar spray on agricultural crops. Greater care will be needed in using these products. Subject to those additional precautions in handling more toxic products, the loss of foliar use of heptachlor would create no adverse economic impact.

I.B.1.b. Home Gardens and Ornamentals - Following the Federal Register notice on chlordane and heptachlor, there were no significant requests to continue foliar applications of heptachlor for home gardens, ornamentals, shade trees, and flower garden plants. All foliar uses of heptachlor on home gardens and ornamentals have alternate pesticides. Some of the less long-term hazard to man and the environment than heptachlor, when used as foliar sprays. Loss of these foliar uses of heptachlor would create no adverse economic impact.

I.B.1.c. Field and General Foliar Treatments - This use includes the foliar application to ditchbanks, field borders, roadsides, and vacant lands. Adequate alternate pesticides are available for this use. The available alternates represent less long-term hazard to man and the environment than heptachlor when used as a foliar treatment for these purposes. Loss of these treatments would create no adverse economic impact.

I.B.2. Soil Applications - There is a serious need for heptachlor to control soil insect pests in agricultural crops, lawns, commercial turf, nursery plant stock, and around homes and premises (termites). Insect pests for which heptachlor is needed include ants, wireworms, white grubs, Japanese beetle grubs, white-fringed beetle larvae, cutworms, and termites. Alternatives other than certain chlorinated hydrocarbon pesticides are not registered for all uses nor are they likely to give acceptable control of all the above pests. The loss of the currently registered insecticidal uses of heptachlor as soil applications would have significant impact.

Soil application of heptachlor presents more of a hazard to human health, wildlife, and the environment than seed treatment use. The granules are ordinarily applied to crops, including corn, as a band over the row for control of pests such as corn rootworms, wireworms and white grubs. The treated areas are at least 7-in wide and the pesticides are often applied from a device mounted on the planter. Granules are dropped just ahead of the press wheel for proper insertion into the soil. Most agricultural granules contain 5% to 20% active toxicant. The following are the significant advantages for the use of the granules in minimizing environmental contamination: (1) doses of pesticides in granular form may be kept at a minimum because of reduced drift potential; and, (2) contamination of the edible part of a crop is minimized because of the more specific placement of the pesticide before the crop emerges or before the edible parts are present.

I.B.2.a. Agricultural Crops - More than 53 million acres of corn were harvested in the North Central Region of the United States in 1970. This area is still using large amounts of aldrin, dieldrin, and heptachlor for soil insect control in corn. Presently, at least one-half of the Kansas acreage of corn is probably still being treated with aldrin or heptachlor, especially in communities not experiencing organochlorine pesticide resistance.

The U.S. Department of Agriculture Economic Research Service (Administrative Report May 26, 1972, appended) reported that the total cost to United States farmers for discontinuing the use of heptachlor in 1971 would have been $2.0 million ($1.1 million for substitute insecticides and $0.9 million for production losses). The added cost for substitute insecticides to control rootworms in corn was estimated to be $1.55 per acre. The total added cost per acre for replacing heptachlor in soil insect control programs, other than rootworms, would be $3.89 per acre. The added cost for replacing heptachlor seed treatments with alternative pesticides would be about $28,000.

Increased use of heptachlor may result from the cancellation of the soil insect control uses of other chlorinated hydrocarbon pesticides such as chlordane, aldrin or dieldrin. Present evidence suggests that any added soil use of heptachlor could increase its impact upon the environment.

I.B.2.b. Seed Treatments and Transplant Water - Alternatives other than the chlorinated hydrocarbon insecticides are not registered for all seed treatment uses nor are they likely to give the same acceptable degree of control which is available with heptachlor on the various seeds to be protected. Diazinon® is the only nonchlorinated hydrocarbon insecticide available. The registered uses for Diazinon® are limited.

Seed treatment presents a low order of hazard to human health, the environment, and to wildlife, except for possible injury to buds. The treatment procedure usually involves the application of the pesticide directly at a relatively low dosage rate at a location remote from the field. This treatment is usually carried out by a commercial seed treatment company. However, in some instances the pesticide is placed directly into the furrow along with the seed. In either instance the furrow is covered with soil, thus keeping the pesticide localized.

Transplant water treatments are relatively similar to seed treatment insofar as environmental hazards and the availability of alternatives are concerned Again, diazinon is the nonchlorinated hydrocarbon pesticide that is available in some cases as an alternate. Small quantities of heptachlor are required in transplant water and the chemical is covered with soil.

I.B.2.c. Lawns, Commercial Turf and Nursery Plant Stock - Alternatives other than the chorinated hydrocarbon pesticides are not registered for all uses nor would they be likely to give acceptable control in all cases. The pests involved are ants, sod webworms, chinch bugs, and other soil insects. Increased use of heptachlor could result from cancellation of soil insect control uses of other chlorinated hydrocarbon pesticides such as aldrin and dieldrin. Loss of the currently registered insecticidal uses of heptachlor as a soil application to lawns, commercial turf and nursery plant stock will

There have been numerous indications of the need to continue the uses of heptachlor for control of soil insect pests for these purposes. It has been estimated that the loss of chlordane and heptachlor for turf use would result in damage estimated at approximately $0.50 per square foot in Pennsylvania. One acre of lost turf would cost approximately $20,000 to replace or renew. Turf grass is a primary agricultural industry in Pennsylvania, and the loss of heptachlor for soil insect control would be significantly damaging to the agricultural industry of the state. South Carolina has reported that heptachlor is an alternative for the quarantine and control of Japanese beetles and white-fringed beetles.

I.B.2.d. Termite Control - Heptachlor is registered as a termite soil poison to be used in and around domestic and commercial premises. Termite control is one of the major uses of heptachlor. Alternatives other than the chlorinated

hydrocarbon insecticides are not available. Loss of this use of heptachlor would have a significant impact.

Subterranean termite control with heptachlor is a modified soil treatment use. Less than 1% (330,000) of the total dwellings subjected to termite attack currently receive treatments for the prevention of damage by these pests. The total cost of termite control is estimated to be not less than $250 million per year. One-third of this cost is for damage repairs and the other two-thirds for chemical treatment. In addition, termites do considerable damage to utility poles, fence posts, and other wooden items, with an annual cost probably exceeding $500 million. In general, heptachlor is applied to the soil at critical areas around and under the house. It is applied to the soil before pouring the cement for slab construction. Also, it is applied to the soil and into the subsoil in trenches around the foundations of "basement construction" homes. The chemical may also be used along the foundations of crawl-space homes.

I.B.2.e. Baits - Heptachlor baits are not considered to be essential because other registered materials have the same spectrum of pest activity and present less enviornmental hazard. Loss of the currently registered uses of heptachlor in bait formulations would not have a significant economic impact.

I.B.3. Household and Commercial Uses - This use includes interior spot treatment with residual sprays for control of cockroaches, ants, ticks, and a number of other household and commercial building pests. The insecticide treatments for pest control are usually applied inside the buildings including kitchens and food service areas. Only limited spot residual usage has been registered.

The household use of heptachlor is regulated by interpretation number 23 of the regulations for the enforcement of the Federal Insecticide, Fungicide and Rodenticide Act, 1947. Liquid and pressurized products which deliver a coarse spray are allowable. These products contain not over 0.5 percent heptachlor. Directions for use are for spot treatment only to cracks, [illegible] of other areas where the insects run, rest or hide. Dusts are not registered. Also, claims for space spraying in the air or for use in fine mist sprayers are not acceptable. There are no claims or directions which might lead to contamination of foods.

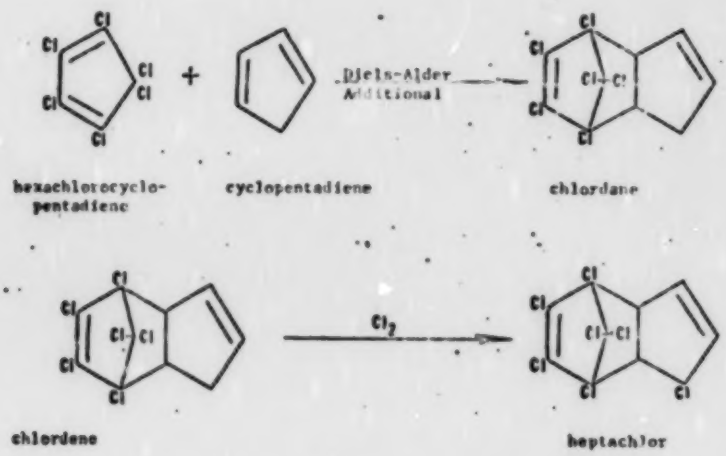
I.B.4. Mosquito Larvicide - Heptachlor has been registered as a mosquito larvicide for many years and constitutes an unnecessary direct contamination of water. Alternatives include Paris green, carbaryl, malathion, naled, pyrethrins, parathion, and Flit MLO. Loss of the use of heptachlor as a mosquito larvicide would have no significant impact on the public health.

CHAPTER II

Chemistry and Analytical Methods

The chemical heptachlor is 1,4,5,6,7,8,8-heptachloro-3a,4,7,7a, tetrahydro-4, 7-methanoindene, which has an empirical formula $C_{10}H_5Cl_7$ with an elemental analysis C=32.17%, H=1.35% and Cl=66.48%.

II.A. Chemical Synthesis and Reaction - Heptachlor is produced commercially by selective chlorination of chlordene ($C_{10}H_5Cl_6$, mol. wt. 339). The general chemical reaction is illustrated as follows:



The mixture produced by this process is technical heptachlor which contains 70-73% heptachlor, 20-23% gamma or trans-chlordane ($C_{10}H_5Cl_8$, mol. wt. 410), 4.5-5.0% δ -trichlorochlordene ($C_{10}H_5Cl_9$, mol. wt. 444.5) less than 1% of an initial reactant hexachlorocyclopentadiene and traces of chlordene.

Brooks (1974) has written an extensive review of the chemistry of chlorinated insecticides including heptachlor.

Chemical reactions of heptachlor, including additions, substitutions, oxidation and reductions were examined as means of preparing derivatives which could be separated and quantitated in the presence of other chlorinated dienes. Chlordane, pentachlorochlordene, acetoxychlordene, and hydroxychlordene have been prepared under specific conditions (Cochrane and Chau, 1968a, 1970; Chau and Cochrane, 1969, 1971; Chau, 1970).

II.B. Physical and Chemical Properties - The technical heptachlor is a light-tan waxy solid with an odor of camphor. The 99% pure chemical heptachlor is a white crystalline solid with a mild odor of camphor of cedar. Both the technical and pure chemical are stable in daylight, air, moisture, and moderate heat, and are nonflammable. The pure compound is stable upon

heating to 160°C. The physiocochemical data of heptachlor, technical heptachlor and heptachlor epoxide are shown in Table 1 and solubility data in Table 2.

II.C. Photodecomposition - Photodecomposition has been investigated since the volatility of heptachlor affords possible additional contamination of the environment. Substances derived from heptachlor are described by formula in the Figure 1. A product, believed to be identical to a caged isomer which is formed when heptachlor is exposed to sunlight, has been formed by ultraviolet irradiation (Rosen, 1969; Benson et al., 1971; Vollner et al., 1971). This is designated photoheptachlor.

Rotenone and pyrethrin have been reported to enhance photoisomerization (Rosen, 1961). Dechlorination occurs when low concentrations of heptachlor in hexane or cyclohexane are irradiated for short periods of time (McGuire, 1971). Hydrogen migration and ring closure, and rearrangement from the epoxide to the keto form without loss of chlorine occurs when heptachlor epoxide is irradiated. The cage derivative of heptachlor (photoheptachlor) is more toxic to insects and fresh water animals, but information on mammalian toxicity is limited (Georgacakis et al., 1971).

Korte examined the photodecomposition of some components of chlordane in acetone solution, and observed a high conversion of heptachlor, heptachlor epoxide, beta-dihydro-heptachlor and chlordane to cage-type compounds. Trans-chlordane did not yield a product even after 100 hr (Hill, 1970).

Benson et al. (1971) found that chlordene, cis-chlordane, heptachlor and heptachlor epoxide were converted on photolysis to cage-type compounds, and isolated them. The materials were irradiated in acetone solution using filters, and as thin films by sunlight, or by UV lamps.

II.D. Analytical Methods - Several multiresidue analytical systems are used for measurement of heptachlor and heptachlor epoxide as residues. As an example, hexane extracts are partitioned with acetonitrile, fractioned on Florisil, identified and quantitated by gas chromatographic techniques, using electron capture or flame ionization detection, and verified by thin layer or paper chromatography. Various modifications of these techniques as reported in the Pesticides Analytical Manual (U.S. Department of Health, Education, and Welfare, 1971) and the analytical methods manual of the Association of Official Analytical Chemists (AOAC, 1970, Method 29.001) are sensitive to 0.001-0.002 ppm heptachlor or heptachlor epoxide in milk and meat and 0.01-0.02 ppm in agricultural food crops. The group of industrial compounds called polychlorinated biphenyls (PCB) interfere on commonly used GLC columns with practically all organochlorine insecticides.

AOAC methods for formulations of heptachlor are the active chlorine method involving reaction with silver nitrate-acetic acid solution (par. 6.237-6.239) and the gas chromatographic method (par. 6.240-6.246) (AOAC, 1970).

Table 1. Physiochemical Properties of Heptachlor

Name	Molecular Weight	Melting Point (°C)	Boiling Point (°C)	Density g/ml	Vapor Pressure mm/Hg	Viscosity Centistokes/ °C
Heptachlor 99% pure	373.5	93 (95-96)	135-145 at 1-1.5 mm Hg	1.65-1.67 77°C	$3x10^{-4}$ at 25°C	-
Technical heptachlor	-	46-74	-	1.65-1.67 at 65°C	$3.75x10^{-3}$ at 50°C and $1.5x10^{-2}$ at 65°C	44-66 at 71°C
Heptachlor epoxide 99.5% pure	389.3	160-161.5	-	-	-	-

Table 2. Solubility - g/100 ml at 27°C
(except when otherwise indicated)

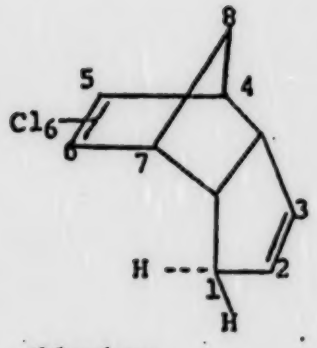
Name	Water	Alcohol	Kerosene	Xylene	CCl_4	Acetone	Benzene
Heptachlor 99% pure	0.056 ppm	4.5	-	102	112	75	106
Technical heptachlor	0.01	4.5	18.9	40	-	75	106
Heptachlor epoxide 99.5% pure	Insoluble	-	-	-	-	-	-

Various confirmatory tests of heptachlor have been developed as a source of additional information on corroboration with residue identity. These chemical methods are summarized in Table 3.

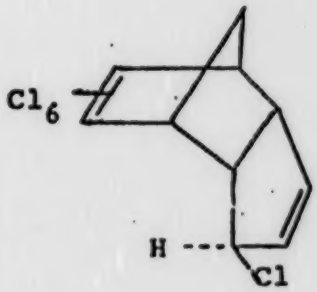
Table 3. Various Chemical Methods for Confirmation of Heptachlor and its Epoxide Residues

Pesticides	Reaction Utilized	Limit of Detectability (ppm)	Pesticide Interference	Reference
Heptachlor	a) Allylic acetylation	0.01	-	Cochrane and Chau (1968a)
	hydroxylation	0.01	Aldrin	
	dechlorination	0.01	Chlordene	Cochrane and Chau (1970)
	b) Addition	0.03		Chau and Cochrane (1969)
	c) Epoxidation	0.05	Heptachlor epoxide	Sans (1967)
Heptachlor epoxide	Epoxide rearrangement	0.01		Cochrane (1969)

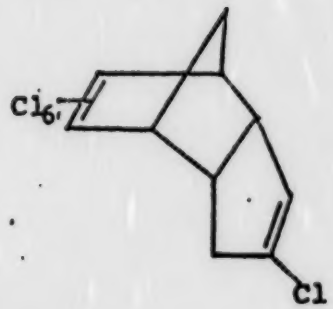
As shown in Figure 1, the presence of a reactive allylic chlorine atom in the heptachlor molecule has been the basis of three confirmatory tests based on its ease of replacement. Of the common organochlorine pesticides, heptachlor reacts quantitatively with a silver acetate-glacial acetic acid mixture and yields 1-acetoxychlordene which, with the GLC conditions used, had a retention time close to heptachlor epoxide. When the reaction of heptachlor with silver salts was extended to silver carbonate in aqueous alcohol, 1-hydroxychlordene was obtained which could easily be converted to more volatile and GLC-responsive silyl ether. This silyl ether, unfortunately, has an Rt identical to aldrin. It is noted, however, that heptachlor is the only chlorinated pesticide to undergo modification with silver-carbonate and to date (Cochrane and Chau, 1968a) this reaction is the most specific confirmatory test observed for the organochlorine pesticides investigated. The soluble silver salt of heptachlor is reacted with $Cr\ Cl_2$ solution for the allylic dechlorination of heptachlor to chlordene. Cochrane and Chau (1970) described the reaction pathways as shown in Figure 2. The two secondary products (dimer and 1-hydroxychlordene) present give no observable GLC interference. Miles et al., (1969) reported that chlordene has been formed by dechlorination of heptachlor by bacteria and subsequent microbial epoxidation to chlordene epoxide in soils; therefore, interference can occur in such soil sample specimens depending upon the degree of chlordene degradation.



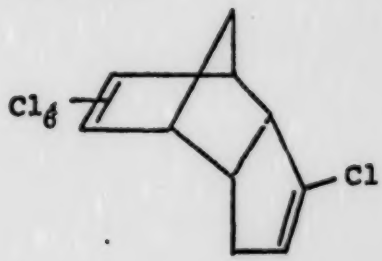
Chlordene



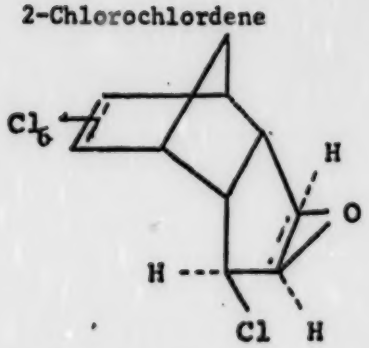
Heptachlor



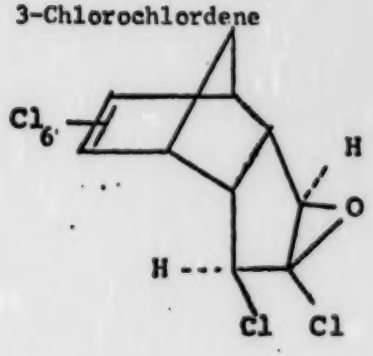
2-Chlorochlordene



3-Chlorochlordene



Heptachlor epoxide



1,2-Dichlorochlordene epoxide

Figure 1.

Structure and Numbering for Some Chlordane Related Compounds

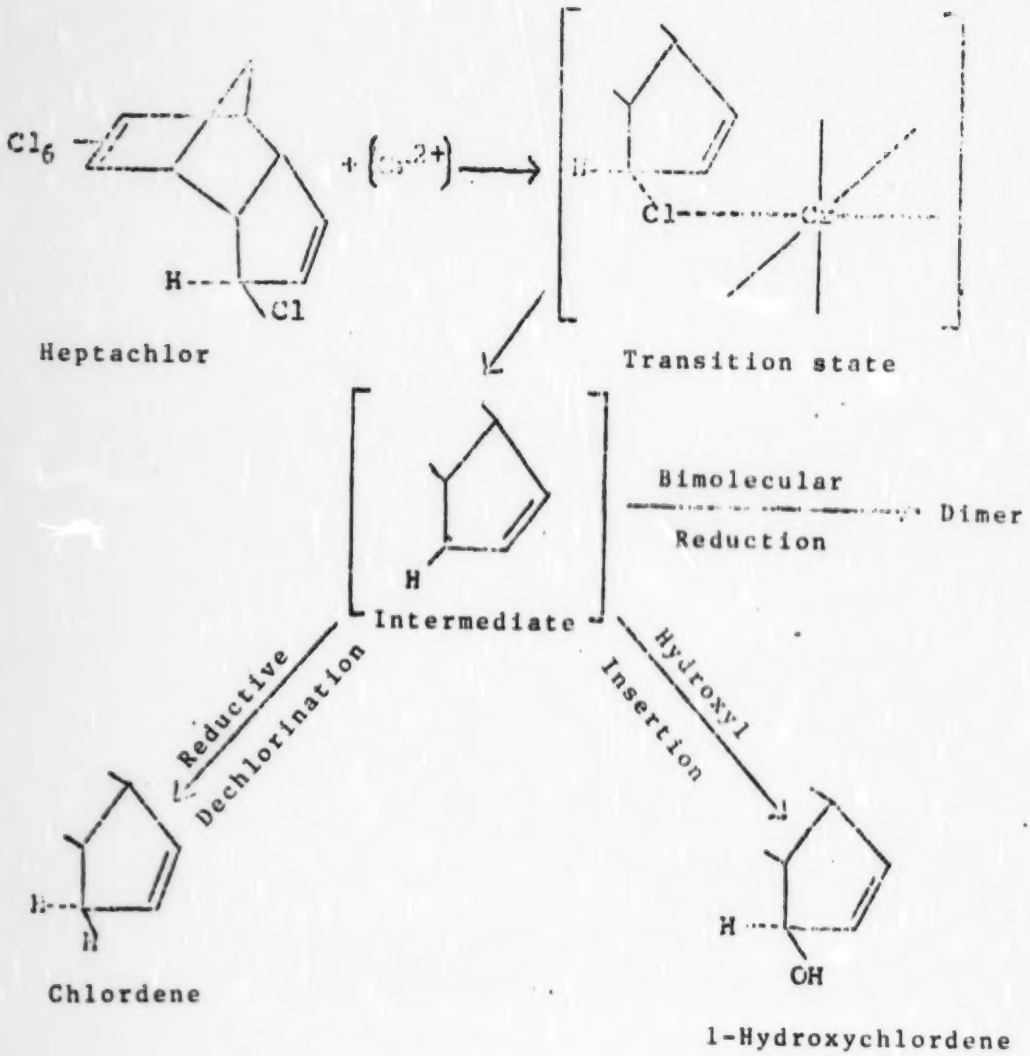


Figure 2.

Reaction Pathways of Heptachlor With Aqueous $CrCl_2$ Solution

Heptachlor is also resistant to epoxidation by peracids but both addition and epoxidation is readily done chemically with tert-BuOCl/HOAc and CrO_3 oxidation respectively. The addition of tert-BuOCl to yield a single derivative peak which has been identified as the corresponding chloroacerate, requires an excess of glacial acetic acid (Chau and Cochrane, 1969).

In the absence of the heptachlor epoxide the confirmatory identification test most used for heptachlor is oxidation. This is carried out using chromic acid to yield heptachlor epoxide (Singh, 1969). The simultaneous identification of heptachlor and heptachlor epoxide mixture by this oxidation procedure fails because of substantial degradation of the epoxide compound to acidic products. This, however, can be achieved during cleanup using a florisil column for their separation or subsequently using TLC. In combination, heptachlor and its epoxide can be simultaneously confirmed with strong basic reagents. Using potassium tertiary butylate in tertiary butyl alcohol, heptachlor produces 1-hydroxychlordene whereas heptachlor epoxide undergoes rearrangement to secondary alcohol, 1-hydroxy-3 chlordene. Both derivatives can be converted to more GLC-responsive compounds either by silylation or acetylation of the allylic hydroxyl groups. This does not affect any of the accompanying dehydrochlorinated products (Cochrane and Chau, 1968b). The procedures described for acetylation, epoxidation, addition, dehydrochlorination, etc., for the confirmation of identity of heptachlor and its major metabolite, heptachlor epoxide, can also be applied to minor metabolites as shown in Table 3.

The other two confirmatory tests for heptachlor involve addition to the sterically hindered double bond. Generally, chlorine does not add to heptachlor without the presence of an initiator, such as antimony pentachloride.

Table 3. Chemical Derivation Confirmatory Methods For Minor Metabolites of Heptachlor

Parent Pesticide	Metabolite	Group Utilized	Derivative
Heptachlor	a) chlordene	1. allylic hydrogen	1-bromo-chlordene
		2. double bond	chlordene epoxide
	b) 1-hydroxychlordene	1. allylic hydroxy	silyl ether
		2. double bond	chloracetate epoxide
	c) 1-hydroxy-2,2-epoxy-chlordene	1. hydroxyl	silyl ether
		2. epoxide	trihydroxy-chlordane

II.F. Spectroscopic identification methods - The G.L.C. detection system (electron capture or flame ionization) are ultra sensitive but none of the detectors are completely specific and cannot provide an unequivocal identification based only on retention times (Rt). Verification by various independent methods is required for positive identification.

II.F.1. Infrared spectrophotometry - The usefulness of infrared microtechniques in helping establish and confirm the identity of organic chemical pesticides and/or their metabolite(s) or degradation products as residues at microgram level has been well established. Functional group-absorption band correlation charts are well known and routinely used by analysts for characterizing chemicals of unknown identity. The positive identification and confirmation of identity of the unknown is done by exact comparison of the various absorption bands of the unknown with those of a compound prepared synthetically by an unequivocal procedure. Where a synthetically prepared compound is not available for spectrophotometric comparison with the unknown, infrared data in conjunction with mass spectrometric, ultraviolet and nuclear magnetic resonance can allow the deduction of the unknown compound's structure with reasonable assurance.

II.F.2. P-value as a confirmatory test - The P-value, defined as the fractional amount in the nonpolar phase, of pesticides and related compounds is determined by single or multiple distribution between immiscible solvents at 25.50°±0.5°C. (Bowman and Beroza, 1965; and Beroza et al., 1969). This test has been employed as an analytical tool in clean-up, for confirmatory identification of a pesticide, and for selecting solvents for partition clean-up procedures. The P-values in certain solvent systems for heptachlor are shown in Table 4.

II.F.3. Nuclear Magnetic Resonance - There is published literature on the NMR spectra of most of the organo-chlorine pesticides (standard 99% ± pure chemical compounds). Singh (1969) reported that the NMR spectrum of heptachlor epoxide gave one proton doublet at T 6.70 with J-values of 3 and 8 CPS, three proton triplets at T 6.3 with J-value of 3.5 CPS, and multiplet at T 5.70. The low sensitivity and the high cost of instrumentation at ultra micro-levels has precluded the wide acceptance of NMR except as a useful technique in conjunction with other independent measurement methods for positive identification of an unknown compound.

II.F.4 GLC - Mass Spectrometry - The use of GLC-mass spectrometry for the qualitative and quantitative estimation of pesticide residues is one of the most significant advancements in residue analysis in recent years. Francis Biros discusses applications of this technique in a chapter on "Applications of Combined Gas Chromatography - Mass Spectrometry to Pesticide Residue Identifications" in ACS Advances in Chemistry Series 104, "Pesticides Identification at the Residue Level" (1971).

Chlorinated hydrocarbon pesticide residues in human adipose tissue and liver tissue samples have been identified by mass spectrometry coupled with gas chromatography. Biros and Walker (1970) positively showed that the GLC peak

with the retention time for heptachlor epoxide in human adipose tissue was actually heptachlor epoxide and not a derivative of chlordane. The characteristic Mass Spectral Peaks and Intensities for heptachlor epoxide are found to be m/e 81 (100%), 353 (84%), 355 (76%), 351 (48%), 357 (35%), 237 (33%), 386 (molecular ion, 8%). Several individual and and multiresidue analytical methods are available for GLC-Mass spectrometric confirmation and identification of pesticide residues. Evaluation of mass spectral fragmentation pathways provide definitive and conclusive confirmation of residue identity as well as characterization of residues and their metabolites of unknown structure.

Demayo and Comba (1972) reported mass spectra for heptachlor and 1-hydroxychlordene obtained by direct inlet and by inlet from a gas chromatography. The spectra differ greatly depending on the inlet system.

Without highly specific confirmatory techniques such as mass spectrometry it would be difficult to identify some residues. Possibly errors may have been made in the past on the identification of some GLC peaks.

Table 4. P-value of Heptachlor in Different Solvent Systems

	Solvent System					
Rt (relative to Rt of Aldrin)	Hexane Aceto-nitrile	Iso-octane DMF	Iso-octane 85% DMF	Hexane 90% DMSC	Heptane 90% Ethanol	Iso-octane 80% Acetone
0.77	0.55	0.21	0.73	0.77	0.71	0.96

Alpha-chlordane, gamma-chlordane, and particularly oxychlordane and heptachlor epoxide are difficult to separate on most GLC columns. Conder et al. (1972) report that a column containing 1.5% OV 17 plus 1.95% OV 210 will separate all four materials.

Su (1973) determined heptachlor epoxide, oxychlordane and certain other pesticides in the presences of pentachlorobenzines (PCBs) using the Coulsen electrolytic conductivity detector in the non-catalytic reductive mode at 660°C and the column used by Conder et al. (1972). PCBs are not detected under these conditions.

II.E. Chemical Derivatization Technique as a Confirmatory Test - Artifacts of similar electron capture gas liquid chromatography (ECGLC) responses or interfering responses, which include previously unknown derivatives or metabolites, have been reported for heptachlor and heptachlor epoxide.

Chau and Cochrane (1969) reported that the dehydrochlorinated product of trans-chlordane, namely, 2-chlorochlordene (shown in Figure 1) from technical chlordane-treated cabbage have EC-GLC and thin-layer chromatography (TLC) characteristics similar to heptachlor. This illustrates the need for confirmatory identification of GLC peaks. To date no suitable GLC column has

been obtained that will successfully separate these two compounds and, further, it is not known whether the 2-chlorochlordene originated as a minor constituent of technical chlordane or is, in fact, a trans-chlordane metabolite.

Chau and Terry (1974) reported a confirmation method for heptachlor involving reaction in a solid matrix (microcolumn) containing aluminasulfuric acid. The column is heated, then cooled and extracted with benzene. The extract is then gas chromatographed. The derivative, which has not yet been identified, elutes much later than heptachlor.

Stijve and Cardinale (1972) found that heptachlor may be confirmed by spotting a cleaned up extract (0.1 microgram) on alumina, heating to 60°C and gas chromatographing the benzene extract. Heptachlor is converted to 1-hydroxychlordene by this treatment.

A heptachlor epoxide artifact observed by Polen et al. (1970) during a cis- and trans-chlordane feeding experiment in rats (Polen, 1969), has been subsequently identified by Schwemmer et al. (1970) as the closely related compound, 1,2-dichloro-chlordane epoxide. This compound possesses one more chlorine atom in the 2-endo-position than heptachlor epoxide itself as shown in Figure 1.

The four parameters from which the confirmation of identity of a chlorinated hydrocarbon pesticide residue can be inferred with reasonable assurance are 1) Rt (EC-GLC retention time of the pesticide on a given stationary phase), 2) Different retention time (Rt) of a derivative prepared from the pesticide, 3) Rf values of either TLC or paper chromatography (PC), 4) "p" value of solvent solubility.

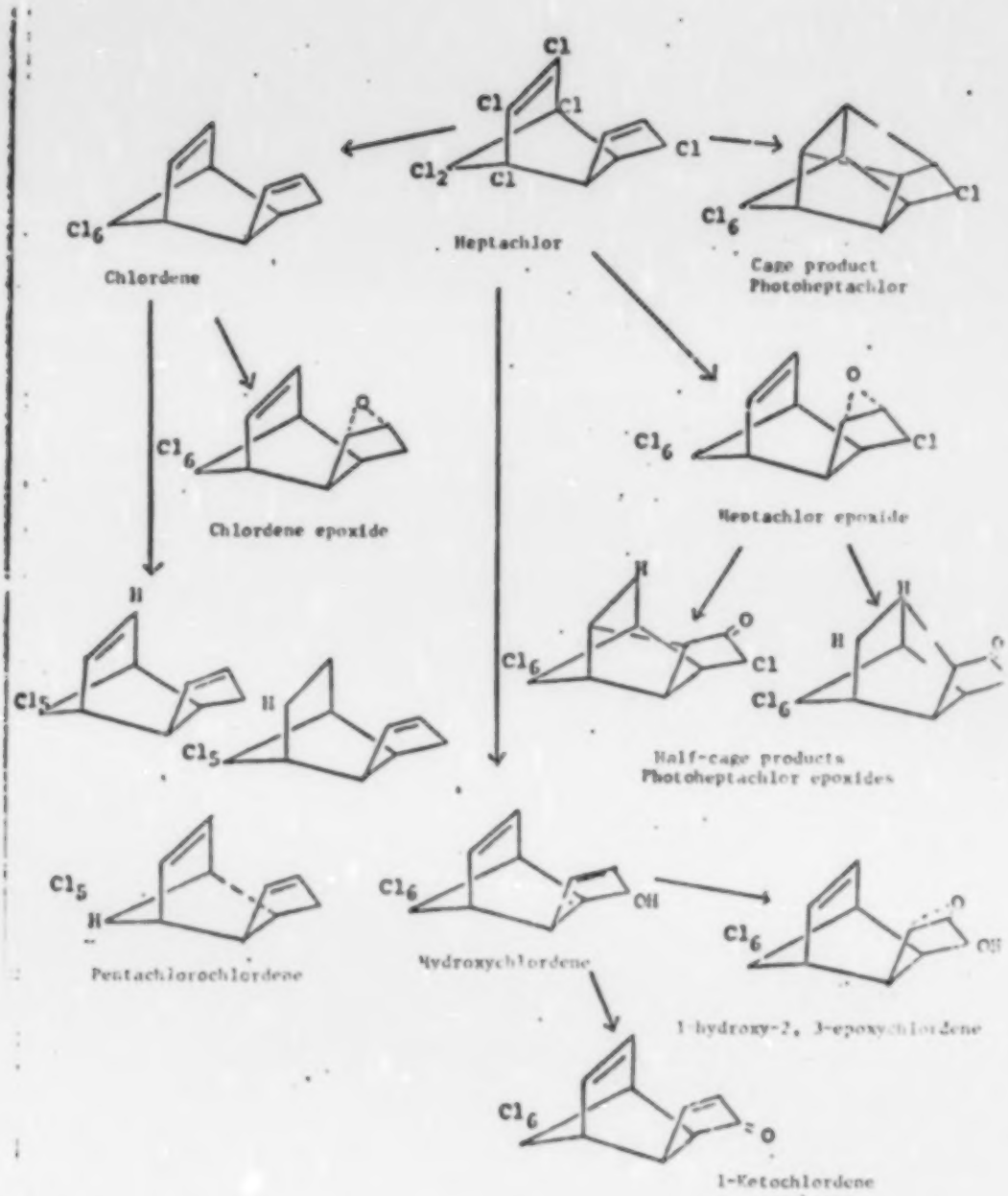


Figure 3.

Substances derived from heptachlor

CHAPTER II

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CHAPTER III

Fate and Implications of Heptachlor in the Ecosystem

The fate and implications of heptachlor in the ecosystem must include a review of the pesticide's distribution in soil, water, air, and related effects upon the flora and fauna of the environment. The distribution and loss of heptachlor from the environment is influenced by various processes such as volatilization, movement with water and absorption and metabolism by plants and microorganisms of the soil.

III. A. The Fate of Heptachlor in the Soil - Retention of heptachlor by soil is influenced by climate, soil type, and management and cropping practices (Harris and Lichtenstein, 1961; Harris et al., 1966; Lichtenstein and Schultz, 1960, 1965; Wilkinson et al., 1964). Retention is longest when the soil remains undisturbed. Following heptachlor applications for uses such as termite control, the penetration of heptachlor into any soil type is influenced by moisture content, and the greatest penetration (25-30 cm) will occur in damp or wet soils (Carter and Stringer, 1970). The greatest amounts of heptachlor are found in the upper 5 cm of soil. The best retention of heptachlor occurs in clay soils or in sandy soil with a high content of organic matter (Carter and Stringer, 1971). Heptachlor and heptachlor epoxide were detected 12 yr after a single application of heptachlor for wireworm control in grasslands of Nova Scotia. The greatest residues were observed from fall applications. The heptachlor penetrated the soil 8-10 in., but 80% remained in the upper 0.4 in (Stewart and Fox, 1971).

In general, the persistence of heptachlor in soils used for diversified agriculture is less than for dieldrin but greater than for lindane or endrin. Studies have also shown that for some time after soil application there will be residues of heptachlor and heptachlor epoxide for plant uptake. Five percent of the total 5 yr application remained as heptachlor epoxide after the fifth annual application of heptachlor at 5 lb/acre to sandy loam soil. Potatoes and carrots were grown in the soils for five successive years without further pesticide treatment. These crops contained residues greater than one-third that amount found in the soil. The residues found were: 0.5 ppm in the soil; 0.35 ppm in carrots; and 0.28 ppm in potatoes. The residues of heptachlor epoxide found in beets, radishes and cucumbers grown in these soils were 5.1, 19.8, and 12.0 percent, respectively, of the measured soil residue (Lichtenstein et al., 1970).

Soil samples were collected from 51 locations in the United States in 1965-1967. The locations included seventeen at which pesticides were used regularly, sixteen locations with a record of at least one application and eighteen locations with no history of pesticide use (Stevens et al., 1970).

Residues of heptachlor were detected only from the areas of regular use. Heptachlor epoxide was found in 24% of the soil samples from fields used for

vegetables, cotton, small grain, and root crops. Recovery of residues could be correlated with history of use, but the amount detected could not be related to rates of application (Mullins et al., 1971).

III.A.1. Degradation of Heptachlor by Soil Organisms - Results from laboratory studies suggest there are two possible pathways for microbial degradation in soil. By one route, heptachlor is converted to chlordene and subsequently epoxidized to 1-exohydroxychlordene and epoxidized to 1-exohydroxy-2, 3-epoxychlordene (Miles et al., 1971). Heptachlor epoxide, chlordene, and 1-exohydroxychlordene have been recovered from field soils.

III.A.2. Translocation to Plants - Grasses and legumes have been found to absorb heptachlor and heptachlor epoxide from the soil residues of the pesticide. Bromegrass, especially the second cutting, was found to contain heptachlor and heptachlor epoxide at amounts equivalent to one-third of the soil residue when grown on heptachlor-treated plots (Beall and Nash, 1969). These toxicants were also absorbed by alfalfa with the greater amounts found in the root crown. Residues found in the stem and leafy portions of the alfalfa were equally distributed.

Soybeans were grown in soil for four consecutive years after a single application of heptachlor and were found to contain approximately 10% of the soil residue. After the fourth year, 15% to 25% of the pesticide applied to the clay loam soil was detected as heptachlor and heptachlor epoxide in plants or soil (Bruce and Decker, 1966).

III.B. Heptachlor in Water - Heptachlor and heptachlor epoxide have not been found in amounts greater than 0.04 ppb in waters of rivers west of the Mississippi River since 1965. Water samples were taken monthly from twenty sampling sites representing major drainage areas during a recent 5-yr. survey and were analyzed for pesticide chemicals. Heptachlor or heptachlor epoxide were found to occur with the least frequency. Heptachlor or heptachlor epoxide were not detected in any water samples obtained from western water sheds after October 1967 (Mangold and Schulze, 1969). Surveys of surface water in the United States after October 1967 (Mangold and Schulze, 1969) did not indicate that residues of heptachlor were major contaminants of surface water. Heptachlor and heptachlor epoxide were not detected in the river waters of the United States after 1968 (Lichtenberg et al., 1970). However, detectable amounts (0.09-0.5) of heptachlor and heptachlor epoxide have been found in storage ponds in some localized areas. (Guerrant et al., 1970).

Translocation of heptachlor from the site of application by water has been investigated in laboratory and field trials and by monitoring open and closed drains from fields where the pesticide had been applied. The vertical movement of heptachlor or heptachlor epoxide through the soil profile was minimal. After four months, 97-99% of the applied insecticide was recovered in the top 15 cm of the soil from treated sites. Organic matter and clay content were factors which limited vertical movement. Slight but detectable leaching occurred in sand (Harris and Sans, 1972).

Heptachlor residues were measured in soil, wells, and run-off waters during four consecutive years of annual application to soil at 0.5 lb/acre in a new irrigation district of Kansas (Knutson et al., 1971). During this period, no buildup of heptachlor residues were noted in soil and no heptachlor or heptachlor epoxide were detected in the wells. Residues no greater than 1 ppm were detected in silt. Heptachlor epoxide was found only once at 5 ppt in surface water. A reservoir and an adjoining river were sampled 18 times during 3 yr. of the study period. Heptachlor was found at 6-10 ppm and heptachlor epoxide was found at 6 ppt in one sample from the reservoir. Heptachlor was found three times at 1-2 ppt in the river.

Plots were treated in Ohio with 2 lb of heptachlor per acre, and only trace amounts of heptachlor and heptachlor epoxide were found in water of two tile drains and two open surface drains from the plots (Schwab et al., 1970).

In water samples taken from treated soils, the insecticide content of the sediment fraction was much greater than that of the water fraction. The heptachlor and heptachlor epoxide content of sediments were found to decrease as the clay content of the soil increased (Sievers et al., 1970).

III.C. Heptachlor in Air - Volatilization of heptachlor begins immediately after application and it will continue at a slower but consistent rate after fixation to soil particles. The volatilization process occurs fast enough to contaminate foliage growing above the application site and to kill insects which are exposed to the vapors. Using Drosophila melanogaster and the house fly as test organisms, it has been estimated that 16% to 38% of the applied toxicant is lost through volatilization. The rates of volatilization of heptachlor are relatively rapid immediately after application to the soil. As the insecticide becomes "bound" to the soil, the volatilization decreases to a constant rate which is influenced by the relative humidity of the air and the soil type (Harris and Lichtenstein, 1961).

Corn leaves from fields treated with 4.6 lb of heptachlor per acre were found to contain 180 ppm heptachlor and heptachlor epoxide. The concentration of heptachlor residues decreased with the height of the plant and with lateral distance from the sites of application. The corn leaves taken 180 cm above ground were found to contain only 20% to 30% of those residues found at 60 cm above ground. The heptachlor residues on corn leaves taken 30 m from the site of application had only 5-10% of the residues of similar leaves from the treated area (Caro, 1971). Similar results were observed for soybeans grown in pots under greenhouse conditions with regulated airflow and protection for individual plants (Nash and Beall, 1970).

Pesticides are transported long distances on dust particles by air currents. Dust from fields treated with chlorinated insecticides was carried by winds from east Dallas, Texas and deposited by rain over Cincinnati, Ohio. The dust deposits recovered from a specially prepared surface in Cincinnati contained 1.34 ppm organic chlorine materials of which 0.5 ppm was chlordane and 0.04 ppm was heptachlor epoxide (Cohen and Pinkerton, 1966).

III.D. Toxicity and Effects of Heptachlor on Birds

III.D.1. Acute Toxicity of Heptachlor - The LD_{50} and LC_{50} values of heptachlor in selected species of birds are presented in Table 1. These data emphasize the variability of toxicity among species.

Table 1.

Toxicity of Heptachlor to Wild Birds

Species	LD_{50} (mg/kg)	LC_{50} (ppm)	
Mallard (male)	2000	-	Tucker and Crabtree (1970)
			Heath et al. (1970)
Bobwhite (quail)	125	450-700	DeWitt and George (1960)
			Heath et al. (1970)
Pheasant	150-400	250-275	DeWitt and George (1960)
			Heath et al. (1970)
Coturnix	-	80-95	Heath et al. (1970)

III.D.2. Heptachlor Effects and Residues for Birds in the Fields - Forty-six sharp-tailed grouse were collected from six counties and 48 pheasants were collected from four counties of South Dakota during 1965-1967. Seventy-four percent of the grouse contained less than 0.01 ppm heptachlor epoxide, and the balance of the birds contained 0.01-1.0 ppm heptachlor epoxide. Seventy-one percent of the pheasants contained 0.01-1.0 ppm heptachlor epoxide, and the balance of the pheasants contained less than 0.01 ppm (Greichus and Greichus, 1968).

Bald and golden eagles found in 18 states and Canada were analyzed for pesticide residues. Dieldrin and metabolites of DDT were found in all specimens whereas heptachlor epoxide (0.05-0.8 ppm) was found in 37 of the 67 birds.

Numerous accounts of population reduction have been reported for birds following the use of heptachlor. A significant decrease in quail population persisted in Georgia for 3 yr after the treatment of land with 2 lb of heptachlor per acre (Rosene, 1965). Applications of one-half pound of heptachlor per acre caused a decline of numbers of cocks and coveys. Bobwhite quail were introduced into areas immediately after application of heptachlor at rates of 2, 1-1/2, and 1/4 pound per acre. The mortalities observed within 15 days were: 61% at 2 lbs; 50% at 1-1/2 lb; and 17% at 1/4 lb (Kreitzer and Spann, 1968).

An aerial application of heptachlor granules was made over a forest preserve consisting of a 25-square mile area. The granules were applied at the rate of 2 lb active per acre for Japanese beetle control. More than 300 birds, including mallards, robins, grackles, starlings, cardinals, cowbirds, meadowlarks, brown thrashers, and house sparrows were found dead in the area over a 2-month period following treatment.

Each year in the area inhabited by these species, a total of three or four dead birds are found. Hundreds of other birds from the thrush, sparrow, and warbler families visited the area during the period of observed mortality without demonstrating any ill effects. One banded robin had 11.1 ppm heptachlor epoxide in tissues. Some mortality among the mammals was also observed (Bartel, 1960).

A program to eradicate the sugarcane root weevil from an urban area in Florida in the Spring of 1969 was studied to assess effects on fish and wildlife. Two basic techniques were utilized: analyses of residue accumulations in selected species and search for dead animals. Results are summarized in Table 2. Residues increased substantially in birds but not in earthworms, fishes, or aquatic invertebrates. Considerable bird mortality followed treatment with granules containing 10% heptachlor applied at 30 lb/acre. Residues in specimens analyzed indicated death from heptachlor poisoning. (Oberheu, 1971).

Table 2. Insecticide Residues in Pre- and Posttreatment Samples of Animals Collected from the Treatment Area

Species Sampled	Collected	PPM INSECTICIDE DDT-DDE-DDD	Dieldrin	Heptachlor Epoxide
Pool of 10 Sparrow brains	Pretreatment	.88	.02	.05
	Posttreatment	.29	.01	.53
Pool of 10 Sparrow carcasses	Pretreatment	1.65	.04	.04
	Posttreatment	.94	.09	1.69
Pool of forage fish	Pretreatment	1.87	.18	.04
	Posttreatment	1.37	.08	.04
Pool of predator fish	Pretreatment	-	-	-
	Posttreatment	1.64	.08	.02
Pool of earthworms	Pretreatment	.09	.01	.01
	Posttreatment	.08	Trace	.04
Pool of aquatic invertebrates	Pretreatment	.22	.05	.03
	Posttreatment	.02	Trace	.00

* (Oberheu, 1971).

III.D.3. Specific Effects of Heptachlor on Fish and Wildlife Following Use to Control Fire Ants - Four farms were surveyed for fish and wildlife effects after treatment with heptachlor at 2 lb AI/acre for fire ant control. The following crustacean, fish and wildlife deaths were observed within 3 weeks after application: 53 mammals consisting of 12 species; 222 birds consisting of 28 species; 22 reptiles consisting of at least eight species; many species of frogs; several kinds of crayfish; and, many fish including eight species (Smith and Glasgow, 1963).

In a 2-yr study carried out to determine the effects of heptachlor on a bird population during fire ant control, the pesticide was applied at 0.25, 0.5, and 2 lb per acre. After application, there appeared to be no arthropod population, and alterations in the behavioral patterns of birds and bird mortality were observed. The nesting and grounddwelling insectivorous birds were most severely affected. Fairly complete recovery of both bird and insect populations occurred 1 yr after the last application of heptachlor (Ferguson, 1964).

In 1957, the U. S. Department of Agriculture, in cooperation with several states, treated approximately 27 million acres with 2 lb active heptachlor per acre for fire ant control. The bird nesting success for a treated study area (May 1958) was only 11.4%, and the nesting success increased to 45.4% in 1959 (Pimentel, 1971).

III.E. Toxicity of Heptachlor to Fish and Other Aquatic Animal Life - Table III.E. summarizes the toxicity of heptachlor to fish and other species of animals which are commonly found in water. In general, these data would indicate that certain species are readily affected by small amounts of heptachlor.

Trout withstood exposures to larger amounts of heptachlor at lower temperatures (Macek et al., 1969). Bluegill growth was reduced in heptachlor-treated (0.05 ppm) ponds, averaging only 7.85 grams after 84 days compared with the controls which grew to 13.5 grams in the same time (Cope, 1966). It was (Andrews et al., 1966) found in an investigation of the persistence of heptachlor in fish that 50% of the chemical was lost in about one month.

Samples of fish were collected from 50 sampling stations located in the Great Lakes and in the major river basins throughout the United States for a study of pesticide residues. Heptachlor and heptachlor epoxide were found with greater frequency among samples taken from the lower Mississippi. Greatest amounts were found in specimens from the Great Lakes and Atlantic areas (0.01-8.46 ppm). Heptachlor or heptachlor epoxide were not detected in specimens from the interior basins, but were found in less than 10% of the specimens from the California streams, Columbia River, Pacific Coast streams and Alaska (Henderson et al., 1969).

Heptachlor and heptachlor epoxide were not detected in 807 composites representing 30 species of fish from the Pacific Ocean (Duke and Wilson, 1971).

Table 3. The LC_{50} of Heptachlor for Arthropods and Various Fishes.

Species	Exposure (hr)	LC_{50} (ppm)	Reference
Fish			
Rainbow Trout (*Salmo gairdneri*)	24	0.250	Mayhew (1955)
	24	0.015	Cope (1965)
Harlequin fish (*Rasbara heteromorpha*)	24	0.090	Alabaster (1969)
Bluegill (*Lepomis macrochirus*)	48	0.026	Cope (1966)
	96	0.019	Henderson *et al.* (1959)
Goldfish (*Carassius auratus*)	96	0.230	Henderson, *et al.* (1959)
Mosquito-fish (*Gambusia affinis*)	48	0.070	Boyd and Ferguson (1964)
Stone fly (*Pteronarcella badia*)	24	0.006	Sanders & Cope (1968)
(*Pteronarcys californica*)	24	0.008	Sanders & Cope (1968)
	48	0.006	Sanders & Cope (1968)
nymph (*P. californica*)	48	6.000	Cope (1966)
(*Claassenia sabulosa*)	24	0.009	Sanders & Cope (1968)
Water flea (*Daphnia pulex*)	48	0.042	Sanders & Cope (1968)
Amphipod (*Gammarus lacustris*)	24	0.150	Sanders (1969)
Sand Shrimp (*Crangon septemspinosa*)	24	0.110	Eisler (1969)
Grass Srhimp (*Palaemonetes vulgaris*)	24	> 6.500	Eisler (1969)
Hermit Crab (*Pagurus longicarpus*)	24	0.470	Eisler (1969)

III.F. Studies of Heptachlor Which Indicate Biomagnification of the Pesticide May Be A Significant Environmental Factor - Oysters exposed 10 days in flowing sea water that contained 0.01 ppm heptachlor concentrated the pesticide in their bodies 17,600 times (Wilson, 1965).

In pond water containing .05 ppm heptachlor, bluegill fish concentrated heptachlor to a level of 15.70 ppm (Cope, 1966).

CHAPTER III

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CHAPTER IV

Residue in Crops and Food Items

The use patterns for heptachlor have changed since its introduction as an insecticide. Prior to 1960, heptachlor was widely used on forage crops, oil crops (seed), vegetable crops, cereal crops, sugar beets and crops such as peanuts. The present uses of heptachlor have been primarily as soil applications and seed treatments.

IV.A. Tolerances - Tolerances for heptachlor have been established by the Environmental Protection Agency in the United States at 0.1 ppm for cabbage, snap beans, lettuce and rutabagas. Zero or extended tolerances are in effect for barley, beans, blackberries, blueberries, boysenberries, chestnuts, citrus, corn, cotton, cranberries, dewberries, oats, peaches, pears, peppers, pineapples, raspberries, rice, rye, sorghum, soybeans, tomatoes and wheat.

Action levels have been established for residues of heptachlor in some foods or crops for which formal tolerances have not been established. These action levels are the Food and Drug Administration's criteria for legal action. The following action levels have been recognized for heptachlor and heptachlor epoxide, individually or in combination: 0.3 ppm for (edible portion only) fish (smoked, frozen, canned or raw); shellfish (smoked, frozen, canned or raw); 0.05 ppm for apricots, blackberries, blueberries, boysenberries, citrus fruit, cranberries, currants, dewberries, elderberries, figs, gooseberries, huckleberries, loganberries, melons, nectarines, pears, plums, quinces, raspberries, strawberries, artichokes, asparagus, beans (except snap beans), broccoli, celery, collards, cucumbers, eggplant, endive, kale, mustard greens, okra, parsley, peppers, pimentos, pumpkins, squash, spinach, summer squash, swiss chard, winter squash; 0.03 ppm for eggs, rice, hay (all not covered by tolerances); and, 0.3 ppm in fat of cattle, sheep, goats, swine, and poultry (Pippen, 1972).

IV.B. Acceptable Daily Intake - The estimate of acceptable daily intake for man has been established at 0-0.0005 mg/kg body weight. Levels of heptachlor causing no significant toxicological effect in experimental animals were: in rats the level was 5 ppm in the diet, equivalent to 0.25 mg/kg body-weight/day; and, in dogs the level was 2.5 ppm in the diet, equivalent to 0.06 mg/kg body-weight/day (FAO/WHO, 1971).

IV.C. Residues in Food - Foods are monitored for pesticide residues through market-basket surveys. Market basket samples for the total diet studies are purchased from retail stores, bimonthly, in five regions of the United States. A shopping guide listing 117 foods for all regions is used, but not all foods are represented in all regions because of differences in regional dietary patterns. The food items are separated into 12 classes of similar foods and prepared for consumption by dieticians. After preparation, the food items are composited into 12 classes of similar foods (e.g., dairy products; meat, fish and poultry; legume vegetables; and garden fruits) for more reliable analysis and to minimize the dilution factor. Each class in

each sample is a composite. The proportion of food items used represents the high consumption level of a 16-to-19-yr-old male. Each sample represents a 2-week supply of food (Duggan, et al., 1971).

Another method of sampling residues is via surveillance samples which are generally collected at major harvesting and distribution centers throughout the United States and examined in 16 FDA district laboratories. Surveillance samples are not obtained in retail markets. Samples of imported food are collected when offered for entry into the United States.

IV.C.1. Recent Market Basket Surveys - Table 1 gives the dietary intake of heptachlor and heptachlor epoxide for 1964-1969 (Duggan et al., 1971). These results obtained during a 5-yr period, June 1964 - April 1969, are compared with the acceptable daily intake (ADI) established by the FAO/WHO Expert Committee. The amounts of these pesticide chemicals calculated from this high consumption diet (FAO/WHO), approximately twice that consumed by a normal individual, are well below the daily intake regarded as safe by the FAO/WHO Expert Committee except for the combined residues of aldrin and dieldrin which have approached the ADI during the period of this study.

Heptachlor epoxide was reported as present in a majority of food groups for samples of domestic food examined during the period of July 1, 1963 - June 30, 1969. A total of 111,296 samples of domestic food were examined (Duggan et al., 1971).

IV.C.2. United States Department of Agriculture Meat and Poultry Sampling - Meat and poultry samples are obtained from animals and poultry slaughtered in all Federally-inspected establishments and from shipments offered for entry into the United States. The samples are examined in seven laboratories of the Consumer and Marketing Service, USDA (Duggan et al., 1971).

Heptachlor and heptachlor epoxide were among the eight pesticide chemicals commonly found in the fat of poultry during the 2-yr period reported (FY 1968-1969). The incidence of DDT, dieldrin, and heptachlor-heptachlor epoxide exceeded those found in any other class of foods.

Data from a total of eight studies on the relationship between the levels of heptachlor and heptachlor epoxide in feed to the levels in meat and milk show that the maximum residue level in animal feed that can be permitted without exceeding the practical residue limits for these animal products is 0.04 ppm of combined residues (FAO/WHO, 1971). Further, FAO/WHO indicated that residues of heptachlor and its epoxide should each be determined and the sum expressed as heptachlor. The tolerances of FAO/WHO apply to residues from application to seed and soil only.

Table 1. Dietary intake of pesticide chemicals

Compound	WHO/FAO Accept. Daily Intake	Mg/Kg of Body Weight/Day Total Diet Studies						
		1965	1966	1967	1968	1969	1970	6-Yr Average
Aldrin		0.00001	0.00004	0.00001	0.00001	0.0000001	0.0000006	0.00001
Dieldrin		0.00008	0.00009	0.00005	0.00005	0.00007	0.00007	0.00007
Total	0.0001	0.00009	0.0001	0.00006	0.00006	0.00007	0.00007	0.00008
Carbaryl	0.02	0.002	0.0005	0.0001	--	0.00004	--	0.0005
DDT		0.0004	0.0005	0.0004	0.0003	0.0002	0.0002	0.0003
DDE		0.0003	0.0003	0.0002	0.0002	0.0002	0.0001	0.0002
TDE		0.0002	0.0002	0.0002	0.0002	0.0001	0.0001	0.0002
Total	0.005	0.0007	0.001	0.0008	0.0007	0.0005	0.0004	0.0007
Dichlorvos	0.004	NOT DETERMINED						
Diphenyl	0.125	NOT DETERMINED						
Gamma BHC (Lindane)	0.0125	0.00007	0.00006	0.00007	0.00004	0.00002	0.00002	0.00005
Bromide	1.0	[1]0.30	[1]0.22	[1]0.29	[1]0.41	[1]0.24	[1]0.24	[1]0.30
Heptachlor		0.000003		0.000001	0.000001	0.000001	0.000001	0.000001
Heptachlor epoxide		0.00003	0.00005	0.00002	0.00003	0.00003	0.00002	0.00003
Total	0.0005	0.00003	0.00005	0.00002	0.00003	0.00003	0.00002	0.00003
Malathion	0.02		0.0001	0.0002	0.00004	0.0002	0.0002	0.0001
Diazinon	0.002		0.00002	0.000001	0.000001	0.000004	0.00001	0.00001
Parathion	0.005		0.00001	0.00001	0.000001	0.00001	0.000003	0.00001
BHC		0.00003	0.00004	0.00003	0.00004	0.00002	0.00002	0.00003
Dicofol (Kelthane)		0.00004	0.0001	0.0002	0.0001	0.0001	0.00005	0.0001
Endrin		0.000009	0.000004	0.000004	0.00001	0.000004	0.0000005	0.000005
Total Chlorinated Pesticides		0.0012	0.0016	0.0012	0.0010	0.0008	0.0006	0.0011
Total Organophosphates			0.00014	0.00025	0.00007	0.00023	0.00026	0.00019
Total Herbicides		0.00012	0.00022	0.00005	0.000006	0.00005	0.000008	0.00008

[1]Total bromides present-includes naturally occurring bromides.

Source: Duggan et al. (1971).

CHAPTER IV

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CHAPTER V

The Toxicology and Epidemiology of Heptachlor

Technical heptachlor is a mixture of compounds consisting of heptachlor, gamma-chlordane, nonachlor, hexachlorocyclopentadiene and traces of octachlor. Since heptachlor is a complex mixture, its toxicity consists of the sum of the intrinsic toxicities of the various components. Accordingly, the toxicity of technical heptachlor will vary as the ratios of its components vary.

V.A. Toxicity to Laboratory Animals - The toxicities of heptachlor, its oxidation product, heptachlor epoxide, and several heptachlor metabolites and analogues have been investigated in certain species in laboratory animals. These studies include, but not for all compounds, the effects of both short-and-long-term administration, the effects on reproduction and the ability of the compound to increase the incidence of tumor formation.

V.A.1. Acute Toxicity - When absorbed in sufficient concentrations into the tissues of experimental animals, heptachlor or its epoxide produce signs and symptoms of toxicity which are related to central nervous system stimulation. These signs and symptoms are characterized by hypersensitivity to auditory or tactile stimuli, ataxia, tremors, lacrimation, salivation, severe clonic and tonic convulsions, respiratory difficulties, weakness, and terminal coma. In some species, depression of body temperature occurs during convulsive seizures. These responses to toxic doses are not influenced appreciably by the route of absorption of the compounds. The time of death may vary from 2 hr to 11 days after administration of the test compound.

V.A.1.a. Acute Oral Toxicity - Numerous studies have been carried out on the toxicity of heptachlor, heptachlor epoxide, and related compounds in experimental animals. The acute oral LD_{50}'s of heptachlor and related compounds appear in Table 1.

V.A.1.b. Acute Dermal Toxicity - Only a limited number of studies have been reported for the dermal toxicity of heptachlor. Gaines (1969) reports heptachlor (in xylene) to have an LD_{50} of 195 mg/kg in male rats and 80 mg/kg in female rats. Lehman (1952) reports an acute dermal LD_{50} of heptachlor (dry powder) in rabbits to be greater than 2000 mg/kg. There was no apparent skin irritation. The animals displayed severe anorexia, hyperexcitability and convulsions. A dermal exposure of 5 hr duration to 940 mg/kg of heptachlor epoxide, 10% solution in peanut oil, caused reduction in rates of growth of male and female rats. In rabbits, four consecutive daily exposures of 5 hr each to 300 mg heptachlor epoxide, dermally, produced a decrease in weight gain (Witherup et al., 1959a).

V.A.2. Subacute Toxicity - For the sake of organization, studies of less than 2 yr duration have been considered under "subacute" toxicity regardless of the species of animal involved.

The effects of the administration of heptachlor or its epoxide to experimental animals for periods of up to 1 yr and qualitatively similar to the administration

Table 1. Acute Oral LD_{50}'s of Heptachlor and Related Compounds

Compound	Animal	LD_{50} (mg/kg)	Reference
Heptachlor	Rat (M)	60(38-95)	Witherup et al. (1959a)
	Rat (F)	142(119-169)	Witherup et al. (1959a)
	Mice (M)	93.9(59.3-148.2)	Wazeter (1971)
	Mice (F)	104.8(71.5-153.6)	Wazeter (1971)
Heptachlor-epoxide in peanut oil	Mice (M)	39.2(32.1-48.0)	Witherup et al. (1959a)
	Rats (M)	61.3(42.1-88.0)	Witherup et al. (1959a)
	Rats (F)	46.5(34.5-62.9)	Witherup et al. (1959a)
	Dogs (M)	8-55*	Witherup et al. (1959a)
	Dogs (F)	16-80	Witherup et al. (1959a)
Heptachlor-epoxide in Methocel	Rat (M)	107(64-178)	Wazeter et al. (1968)
	Rat (F)	142(110-184)	Wazeter et al. (1968)
	Rabbit (F)	110(52-232)	Wazeter et al. (1968)
Heptachlor-epoxide	Mice (M)	41.3(35.4-48.2)	Wazeter (1971)
	Mice (F)	43.6(30.6-62.1)	Wazeter (1971)
Heptachlor+ Heptachlor-epoxide-1:3	Mice (M)	56.2(49.9-63.4)	Wazeter (1971)
	Mice (F)	68.5(55.6-84.3)	Wazeter (1971)
1-hydroxychlordene	Rat	2402	Ingle (1962)
	Rat**	>4600	Mastri et al. (1969)
Nonachlor	Rat	326	Ingle (1962)
Chlordene	Rat**	>4600	Mastri et al. (1969)
3-chlorochlordene	Rat**	>4600	Mastri et al. (1969)
1-chlordene epoxide	Rat**	>4600	Mastri et al. (1969)

*Lethal range
**Groups containing equal numbers of male and female animals.

of the compounds for longer periods of time; the one exception was the incidence of neoplasms. The liver appears to be the target organ, with the extent of alteration increasing with the concentration of the pesticide in the diet and the duration of administration. The alterations include increased liver weight with hepatocellular changes consisting of enlargement of the hepatic cells in the central zone of the lobule. These enlarged cells present aggregation of the acidophilic cytoplasmic granules in the cell periphery. There also appears to be a decrease in the number of these granules. After longer exposure there is an accumulation of lipid matter in the cytoplasm of the hepatic cells. Changes have also been reported in the adrenal medulla and the kidneys of some animals.

V.A.2.a. Subacute Oral Toxicity - Groups of rats, consisting of 25 males and 25 females, were fed diets containing 0 to 2000 ppm 1-hydroxychlordene for up to 224 days. At 110 days three females and three males were separated from each group and mated. The pups were weaned and examined for birth defects. The test compound did not increase the mortality rate among rats of any group during the 224 days of feeding. A male and female at 500 ppm each showed hepatomas; one female at 100 ppm had parotid gland tumors. One control female showed a mammary gland tumor. Histopathological changes were noted in the liver sections from rats at 1,000 or 2,000 ppm. The cytoplasmic margination changes were also evident to some extent in the controls and lower level groups (Ingle 1965).

Rats of unspecified sex (totalling 269) were fed 40, 45, or 60 ppm heptachlor or 35,40, or 45 ppm of heptachlor epoxide or 40, 45, or 60 ppm of a 75:25 percent mixture of the 2 compounds (Stemmer and Jolley 1964). The animals received the chemical diets for a period of 140 days and were then sacrificed at intervals of 10, 20, 30, 60, 80 or 120 days after discontinuance of the chemical diets.

After feeding was discontinued, typical liver lesions regressed. Rats fed a normal diet did not have the typical liver lesions. A significant number of rats sacrificed at 120 days from the 140-day feeding had normal livers. The least recovery level from the liver lesions recurred in the group fed heptachlor epoxide. The largest number of recoveries were among those fed heptachlor.

A second type of lesion was found in some of the rats fed a treated diet for 260 days. It consisted of an enlargement of cells in the periphery of the liver lobule. The boundaries of the cells became predominant and the cytoplasm appeared empty. In most cases both conditions were present in the same liver lobule, separated by a mid-zone of almost normal cells. After the animals were returned to a normal diet, there was no report on whether or not these lesions regressed.

In those cases where the chemical diets were discontinued, an examination of the rats revealed a complete regression of hepatic damage. The medulla showed signs of depletion of catecholamines in the animals that had not recovered and in those animals that were maintained. Cytoplasmic granules in these cells were diminished. Some of the cells exhibited vacuolation within the cytoplasm. The vacuolated cells were primarily in the center of the medulla.

Groups of 10 female rats each were fed 0, 5, or 10 ppm heptachlor for eight months. An examination of liver cells of the groups fed the 10 ppm level

revealed an increase in the smooth endcoplasmic reticulum and the mitochondria (Stemmer and Hamdi, 1964).

Four groups of 10 male and 20 female rats (about 4 months old) each were given daily oral doses of 0, 5, 50 or 100 ppm mg/kg body-weight of pure heptachlor (Pelikan et al., 1968). Administration of the chemical was given for 200 days or until the animals died. All the animals in the groups fed 50 or 100 mg/kg died by the tenth day. The surviving animals in the 5 mg/kg group and the controls were sacrificed for autopsy at day 200.

After 2 days of feeding at the 50 and 100 mg/kg levels the rats developed accelerated respiration. In the 5 mg/kg group, no clinical abnormalities were observed until the fiftieth day, when hyperreflexia, rapid respiration and chronic convulsions were observed. In this group, 2 males and 2 females died before completion of the experiment, as compared with only 1 female in the controls. Weight gain was not affected by the 5 mg/kg dosage.

Gross pathology revealed changes in liver, kidney and spleen. The histopathology showed fatty degeneration of the liver cells, moderate fatty infiltration of the cells of the urinary tubules, and hyperplasia of the smooth endoplasmic reticulum of the liver and spleen.

Ninety-five Wistar rats were given five administrations of 10 mg/kg pure heptachlor in corn oil each by stomach tube, every second day starting at 10 days of age (Cabral and Terracini, 1972). Seven animals died before weaning. No early deaths were recorded among 36 controls given corn oil only. Twenty-nine experimental animals were killed at 60 weeks of age to detect early changes which were nevertheless absent. Growth and survival rates were similar in experimental and control animals.

The incidence of tumors at different sites in males and that of adrenal, thyroid, and pituitary tumors in females were comparable in both groups; 9 of 28 treated females developed a total of 12 tumors in various organs (including 5 mammary tumors and 2 renal lipomatous tumors) whereas 4 of 27 control females developed a total of 4 tumors (2 of which were located in the breast). In view of the different locations of the tumors and the lack of the reproducibility of the finding among males, the results are not considered evidence of carcinogenicity of heptachlor under the present experimental conditions.

V.A.2.b. Subacute Dermal Toxicity - In studies on the dermal toxicities of a number of pesticides, Lehman (1952) studied the effects of daily applications of sublethal amounts of heptachlor to the skin of albino rabbits. Lehman reported that there were no survivors after 14 days of applications of 20 mg/kg heptachlor.

V.A.3. Chronic Toxicity - Witherup et al. (1955) fed CF strain albino rats levels of heptachlor dissolved in ethanol in the diet for 2 yr. Each group of rats, as well as an untreated control, was composed of 20 males and 20 females. The rats were fed levels of 1.5 to 10 ppm heptachlor. Mortality, which was comparable for all groups, did not increase significantly by the presence of heptachlor. Mortality, which was comparable for all groups, did not increase significantly by the presence of heptachlor in any of the concentrations investigated.

The number of tumor-bearing animals was found to be 16/40 at 0 ppm, 9/40 at 1.5 ppm, 13/40 at 3 ppm, 12/40 at 5 ppm, 15/40 at 7 ppm, and 12/40 at 10 ppm. Most tumors were recorded. The only preferential tumor sites were 4 thyroid tumors in the 7 and 10 ppm group.

Velsicol (1966) reported that female albino rats were fed for 2 yr on diets containing a mixture of pure heptachlor and heptachlor epoxide in the ratio of 3:1. The animals were divided into 5 groups which totalled 154. Pituitary and mammary tumors were found at all dose levels, including the controls. The incidence of the tumors varied from group to group, but not in relation to the heptachlor dosage.

All groups, including the controls, showed live histological changes at the end of 2 yr. The changes were: cell enlargement in centrolobular parts, loss of cytoplasmic granules, and appearance of lipid vacuoles. No quantitative differences could be detected between rats given 0 and 5 ppm levels. In other groups, the severity of the changes was related to the dose. Regenerative liver changes were present at 12.5 ppm.

As a portion of a larger study, 100 male and 100 female C3Heb/Fe/J mice were fed diets containing 10 ppm heptachlor or heptachlor epoxide for 2 yr. A similar number of animals served as control. As the mice died during the experiment or were sacrificed at termination, they were autopsied and their viscera were fixed in formalin. The significant findings may be summarized as follows:

	Control	Heptachlor	Heptachlor Epoxide
Surviving 78 weeks	150	135	109
Surviving 2 yr	62	60	19
Hepatic hyperplasia	38	108	65
Benign hepatoma	27	47	85
Hepatic carcinoma	4	4	9

Davis noted that while there were 150 survivors in the control group at 78 weeks with an incidence of 27 benign hepatomas and 4 hepatic carcinomas, there were only 109 survivors in the heptachlor epoxide group with an incidence of 85 benign hepatomas and 9 hepatic carcinomas (Davis, 1965).

V.A.4. Effects on Reproduction - CD strain male and female rats were fed exclusively on diets containing a mixture of heptachlor and heptachlor epoxide in a ratio of 3:1 in amounts of 0, 0.3, 3, or 7 ppm. The rats were mated through three succeeding generations. The number of pregnancies in the F_0 and F_2 generations was slightly reduced in the 0.3 ppm group, but this did not occur at the higher dose levels. A slight increase occurred in the mortality of the pups in the second and third weeks. The other groups did not have a similar increase in the mortality of the pups.

For three successive generations, there was no apparent effect exerted by heptachlor on the fertility of the progenitors or on the ability of the progenitors or the progeny (Witherup et al., 1967).

Groups of 4 male and 20 female chickens were fed dietary levels of 0, 0.2, 0.1 or 0.2 ppm heptachlor epoxide for 25 weeks. Heptachlor epoxide did not influence body weight increase. Mortality was slow in all groups. A slightly higher incidence in the 0.2 ppm group was considered insignificant. Abnormal behavior was also observed.

Records of the weekly egg production and the mean weekly egg weights were not found to be significantly different between the test and control groups. Egg hatchability was slightly decreased for groups fed 0.1 and 0.2 ppm. The heptachlor epoxide did not affect the viability of the hatched chicks (Wolvin et al., 1969).

V.A.5. Teratogenicity - Pregnant female rabbits were orally administered heptachlor epoxide from days 6 to 11 of gestation. Twenty-two rabbits were fed a 0.1 mg/kg body weight/day diet, and 20 rabbits were fed the 5 mg/kg diet. On the 28th day, a Caesarian was performed on the fetuses. No behaviorial abnormalities were apparent. The heptachlor did not also affect body weight gain. No animals died. There were no compound-related effects regarding numbers of viable and nonviable term fetuses, resorptions, empty implantation sites, corpora lutea, or nongravid females.

The treated rabbits had a significant fetus weight increase; the increase was considered compound-related. Heptachlor epoxide was not considered to have affected the survival time. Teratogenic effects were not found to be traceable to the compound (Wazeter et al., 1969).

V.A.6. Carcinogenicity - In the studies carried out with heptachlor epoxide in the rat by Witherup et al. (1959b) and in the mouse by Davis (1965) there was a greater increase in the occurrence of hepatomas in the treated animals than in the untreated controls. Thre was also a suggestion to increase the incidence of heptachlor carcinomas in the Davis study. Based on the Davis study, the Secretary's Commission on Pesticides and Their Relationship to Environmental Health concluded that heptachlor epoxide is positive for tumor induction in the mouse (Mrak, 1969). In their 1970 "Evaluations of Some Pesticide Residues in Food," FAO/WHO concluded that an adequate carcinogenicity study in a second species of animal other than the rat is needed.

V.A.7. Mutagenicity - Various methods are available for mutagenicity testing. From the criterion of presumptive human relevance, methods have been categorized within ancillary submammalian systems and definitive mammalian systems. The relevance to humans of data obtained from ancillary test systems is uncertain, in view of factors such as cell uptake, metabolism, detoxification, dosage and method of administration. Mammalian systems entail fewer of these limitations. The mammalian systems include cytogenetics, the hose mediated assay, the specific locus test, and the dominant lethal test. A positive result in any mammalian system represents evidence of a potential mutagenic hazard (Epstein and Legator, 1971).

V.A.8. Metabolism - The data on the metabolism of heptachlor is incomplete. The formation of heptachlor epoxide in vivo in several species of mammals and in vitro using rat and rabbit liver microsomes in the presence of NADPH has been described (Wong and Terriere, 1965; Nakatsugawa, 1965; FAO/WHO, 1967). It was

suggested that heptachlor epoxide might be further metabolized to a diol (Davidow and Radomski, 1953), but the occurrence of such a compound has not yet been demonstrated. However, when 25 μg of ^{14}C-labelled heptachlor was administered to male and female rats, the radioactivity was largely encountered in the feces as heptachlor epoxide, along with a second metabolite; this second metabolite was also encountered in the urine, but heptachlor epoxide was not.

In both rats and rabbits treated with heptachlor, heptachlor epoxide was the main metabolite found in tissues. The urinary metabolite was found to be 1-hydroxy-2,3-epoxychlordene (Korte, 1967; Klein et al., 1968). It is not known if this compound arises via heptachlor epoxide or via a direct hydrolysis of heptachlor first to form 1-hydroxychlordene. The information available on the mammalian metabolism of heptachlor has been reviewed (Brooks, 1969). In experiments with rabbits and pig liver microsomes, the hydration of heptachlor epoxide to a diol has been demonstrated (Brooks and Harrison, 1969) (Figure 1).

V.A.9. Enzyme Induction - The metabolism of various chemical substances is stimulated, both in vivo and in vitro, by many different types of drugs and chemicals and in the environment over 200 drugs and other chemicals, including heptachlor, are known to stimulate drug metabolism in laboratory animals. Several extensive reviews have been published since the mid-1960's on the inductive effects of chemicals on drug metabolizing enzymes in the liver (Kuntzman, 1969; Conney, 1969; Street, 1969; Conney et al., 1969; and Kupfer, 1967).

The drug metabolizing enzymes are located primarily in the smooth endoplasmic reticulum (SER) of the liver cells. These enzymes catalyze the metabolism of drugs by pathways such as hydroxylation, dealkylation, deamination, sulfur-oxidation, azo-link reduction, and glucuronide formation. Studies conducted in the last decade have demonstrated that treatment of animals with drugs, polycyclic hydrocarbons, and chlorinated insecticides increase the activity of liver microsomal oxidative drug-metabolizing enzymes. The most potent inducers of these enzymes are some of the chlorinated insecticides. Single or multiple doses at relatively low levels significantly increase the microsomal enzyme activity in rats.

Heptachlor and heptachlor epoxide were administered to male rats at dietary levels of 0, 1.0 or 5.0 ppm for 2 weeks (aldrin or dieldrin were also fed at the same levels to other groups). After completion of the feeding, the animals were sacrificed and microsomal preparations made from their livers. Microsomal epoxidation, as measured by the epoxidation of aldrin to dieldrin, was unaffected by 1.0 ppm, but was significantly affected by 5.0 ppm of heptachlor or its epoxide. The increase in the rate of epoxidation was correlated to the dietary level and to the concentration of the cyclodiene compounds in the microsomes. Both heptachlor and aldrin appeared to be substrates for the same enzyme, which is inhibited by the epoxide. Microsomal metabolism of the epoxides was not found to proceed further (Gillette and Chan, 1968).

Female rats were fed with heptachlor in the diet a dose level corresponding to 5 mg/kg body weight/day for 3 months. After this period ^{32}P-labelled fenitrothion at a dose of 24 mg/kg body weight was administered in oil per ounce, and radioactive measurements were made (five times during 24 hr) of the total liver activities and of the degradation products in blood and liver. The results were

compared with those of the control group not pretreated with heptachlor. Total activity in the liver of the group pretreated with heptachlor was 50% higher than in the control group, with a maximum of activity after 4 hr. In the control group, the values diminished gradually after the exposure to fenitrothion. The ratio of the oxygen analogue to fenitrothion in the blood and liver suggests that the conversion of fenitrothion to its oxygen analogue is enhanced and accelerated. Results of this experiment demonstrate that pretreatment of rats with heptachlor increases the metabolism of fenitrothion (Mestitzova et al., 1970).

V.B. Human Toxicity and Epidemiology - The toxicity of heptachlor to humans is similar to that of the other cyclodiene insecticides. Based on data derived from experimental animals, heptachlor is 3 to 9 times as toxic as chlordane. The fatal oral dose of chlordane is estimated to be between 6 and 60 g (Hayes, 1963). The fatal oral dose of heptachlor should be much lower than this. The extimated minimal single dermal dose which is required to produce symptoms is 1.2 g/day. The threshold limit for heptachlor in air is 0.5 mg/M³ (Hayes, 1963).

V.B.1. Signs and Symptoms of Poisoning - The signs and symptoms of acute heptachlor poisoning may be expected to be similar to those produced by the other cyclodiene insecticides. Irritability, salivation, labored respiration, muscle tremors, convulsions, and death, with or without an immediately preceding period of deep depression, have been reported to follow the ingestion of toxic amounts of chlordane and should be expected to occur in cases of heptachlor poisoning.

V.B.2. Laboratory Findings - Clinical laboratory tests are usually normal, however, liver function may be impaired as revealed by appropriate tests. A fat biopsy may reveal the presence of a cyclodiene derivative (Dreisbach, 1963).

V.B.3. Treatment - Depending on the condition of the patient, attention should first be given to sedation or to the removal of the heptachlor which may have been ingested. Syrup of ipecac, gastric lavage, and saline laxatives may be used. Oil laxatives should be avoided since they may increase the absorption of heptachlor. Convulsions may be controlled by the use of barbiturates alone or in conjunction with calcium gluconate (Hayes, 1963).

V.B.4. Human Poisonings - The clinical picture of human poisonings reported for heptachlor has been complicated by the presence of other toxic pesticides in the ingested formulations.

V.B.5. Epidemiological Studies - Studies have been conducted in the attempt to relate organochlorine pesticide concentrations in human fat with the geographic location. Samples of human fat collected from Arizona, Kentucky and Washington were shown to contain low levels of BHC and easily detectable amounts of dieldrin. Heptachlor epoxide was detected in 25 specimens from New Orleans, but none was found in samples from other cities which were cited for comparison (Dale and Quinby, 1963).

Heptachlor epoxide was found in all specimens of adipose tissues taken from 123 persons from the Union of South Africa and trace amounts were found in 12 different types of human tissues obtained at autopsy in Hawaii. The highest total residues of organochlorine insecticides were from those subjects with evidence

of emaciation, resulting from carcinoma or extensive local or generalized pathologic conditions of the liver (Wasserman et al., 1970). Five hundred and five samples of human tissue were analyzed in an attempt to correlate pathological tissue changes with pesticide concentration in fat. No heptachlor epoxide was detected in 35 specimens, 93 contained trace amounts, 17 contained 0.10-0.29 ppm, and 7 contained 0.50-0.74 ppm (Hoffman et al., 1967).

The distribution of chlorinated pesticides in the plasma of pregnant women and in the milk of lactating women was compared with the amounts found in the plasma and tissues of stillborn or newborn infants. The concentration of heptachlor epoxide in the plasma and milk of pregnant or lactating women was found to be 0.03 ± 0.0001 and 0.0007 ± 0.0003 ppm, respectively (Curley and Kimbrough, 1969). In an earlier study, milk from lactating women was found to contain 0.0027 ppm heptachlor epoxide. The organs of stillborn infants contained 0.80 ± 0.30 ppm heptachlor epoxide and the blood of newborn infants contained 0.001 ± 0.0002 ppm (Curley et al., 1966).

In 53 human milk fat samples, the average total DDT content was 2.60 ppm. The values for lindane and heptachlor epoxide were 0.08 and 0.16 ppm, respectively. The level of total DDT was higher in samples from mothers nursing for the first time, but no information was available on the initial pesticide burden of the mothers. The relationship did not hold for lindane or heptachlor epoxide. Only eight of the samples analyzed had total DDT concentrations below the 1.25 ppm tolerance established in the Code of Federal Regulations for milk fat of dairy cattle. Heptachlor epoxide and lindane have zero tolerances in cow's milk. The possible health hazards of these levels cannot be predicted at this time (Kroger, 1972).

CHAPTER V

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